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This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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INVENTOR(S)

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☒ Additional inventors are being named on the 1 separately numbered sheets attached hereto**TITLE OF THE INVENTION (500 characters max)**COMPLETE BIOSYNTHETIC GENE SET FOR SYNTHESIS OF POLYKETIDE
ANTIBIOTICS, INCLUDING THE ALBICIDIN FAMILY, RESISTANCE GENES, AND
USES THEREOF

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☐ Application Data Sheet. See 37 CFR 1.76☐ Other (specify)**METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT**☒ Applicant claims small entity status. See 37 CFR 1.27.☒ A check or money order is enclosed to cover the filing fees☐ The Commissioner is hereby authorized to charge filing
fees or credit any overpayment to Deposit Account Number:☐ Payment by credit card. Form PTO-2038 is attached.FILING FEE
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Respectfully submitted,

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Attorney Docket 79-1

In the UNITED STATES PATENT and TRADEMARK OFFICE

APPLICATION OF M. ROYER, D. W. GABRIEL, R. FRUTOS AND P. ROTT

**COMPLETE BIOSYNTHETIC GENE SET FOR SYNTHESIS OF POLYKETIDE
ANTIBIOTICS, INCLUDING THE ALBICIDIN FAMILY, RESISTANCE GENES, AND
USES THEREOF**

TECHNICAL FIELD

The invention is in the field of genetic engineering, and in particular the isolation and expression of the biosynthetic genes that produce a family of antibiotics known generically as albicidins.

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BACKGROUND OF THE INVENTION

U.S. Patent No. 4,525,354 to Birch and Patil described a "non-peptide" antibiotic of M.W. "about 842" called "albicidin". Albicidin is described as produced by culturing chlorosis-inducing strains of *Xanthomonas albilineans* isolated from diseased sugarcane, and mutants thereof. The antibiotic was isolated from the culture medium by adsorption on resin and was purified by gel filtration and High Performance Liquid Chromatography (HPLC). The chemical structure of this antibiotic was not determined and remained unknown, although the Birch and Patil patent disclosed spectral data for a fraction having antibiotic activity and the presence of approximately 38 carbon atoms and at least one COOH group. The present invention describes and characterizes the family of antibiotics that is produced by culturing chlorosis-inducing strains of *X. albilineans* and mutants thereof, together with the complete set of twenty biosynthetic genes capable of producing the unique and previously uncharacterized family of antibiotics produced by *X. albilineans* and previously lumped together as "albicidins". The set of twenty biosynthetic genes isolated, purified and cloned from a culture of *X. albilineans* revealed that this set of biosynthetic genes is capable of synthesizing products exhibiting a high level of variation among the products, indicating that albicidins comprise a family of polyketide antibiotics. The albicidins described in the present invention are synthesized by twenty genes, including one polyketide-peptide synthase, one polyketide synthase and two peptide synthases, but the substrates of the polyketide-peptide synthase and of one peptide synthase are not α -amino acids. The biosynthetic enzymes represent a previously undescribed and unique polyketide antibiotic biosynthetic system.

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Xanthomonas albilineans is a systemic, xylem-invading pathogen that causes leaf scald disease of sugarcane (interspecific hybrids of *Saccharum* species) (Ricaud and Ryan, 1989 ; Rott and Davis, 2000). Leaf scald symptoms include chlorosis, necrosis, rapid wilting, and plant death. Chlorosis-inducing strains of the pathogen produce several toxic compounds. The major toxic component, named albicidin, inhibits chloroplast DNA replication, resulting in blocked chloroplast differentiation and chlorotic leaf streaks that are characteristic of the plant disease (Birch and Patil, 1983, 1985b, 1987a and 1987b). Several studies established that albicidin plays a key role in pathogenesis and especially in the development of disease symptoms (Wall and Birch, 1997; Zhang and Birch, 1997; Zhang *et al.*, 1999; Birch, 2001).

The prior art indicates that albicidin inhibits prokaryotic DNA replication and is bactericidal to a range of gram-positive and gram-negative bacteria (Birch and Patil, 1985a). Albicidin is therefore of interest as a potential clinical antibiotic (Birch and Patil, 1985a). However, low yield of toxin production in *X. albilineans* has slowed down studies into the chemical structure of albicidin and its therapeutic application (Zhang *et al.*, 1998). The chemical structure of this albicidin remains unknown, however this albicidin has been partially characterized as a non-peptide antibiotic with a molecular weight of about 842 that contains approximately 38 carbon atoms with three or four aromatic rings, at least one COOH group, two OCH₃ groups, a trisubstituted double bond and a CN linkage (Birch and Patil, 1985a; Huang *et al.*, 2001).

Molecular cloning and characterization of the genes governing the biosynthesis of albicidin is of considerable interest because such information indicates approaches to engineer overproduction of albicidin, to characterize its chemical structure, to allow therapeutical applications and to clarify the relationship between toxin production and the ability to colonize sugarcane. Two similar mutagenesis and complementation studies have been conducted to identify the genetic basis of albicidin production in *X. albilineans* strains isolated in two different geographical locations, Australia and Florida.

One study of *X. albilineans* strain LS155 from Australia revealed that genes for albicidin biosynthesis and resistance span at least 69kb (Wall and Birch, 1997). Subsequently, three genes required for albicidin biosynthesis were identified, cloned and sequenced from two Australian strains of *X. albilineans* (LS155 and Xa13): *xabA*, *xabB* and *xabC* (Huang *et al.*, 2001; Huang *et al.* 2000a, 2000b). The *xabB* gene encodes a large protein with a predicted size of 525.6 kDa, with a modular architecture indicative of a multi functional polyketide synthase (PKS) linked to a nonribosomal peptide synthetase (NRPS) (Huang *et al.*, 2001). The *xabC* gene, located immediately downstream from *xabB*, encodes an S-adenosyl-L-methionine (SAM)-dependent O-

methyltransferase (Huang *et al.*, 2000a). The *xabA* gene, located in another region of the genome, encodes a phosphopantetheinyl transferase required for post-translational activation of PKS and NRPS enzymes (Huang *et al.*, 2000b).

5 These first results demonstrated that the albicidin biosynthesis apparatus is a PKS and/or NRPS system. Such systems assemble simple acyl-coenzyme A or amino acid monomers to produce polyketides and/or nonribosomal peptides (Marahiel *et al.*, 1997; Cane, 1997; Cane and Walsh, 1999). These metabolites form very large classes of natural products that include numerous important pharmaceuticals, agrochemicals, and veterinary agents such as antibiotics, immunosuppressants, anti-cholesterolemics, as well as antitumor, antifungal and antiparasitic agents. Genetic studies of prokaryotic PKS and NRPS produced detailed information regarding the function and the organization of genes responsible for the biosynthesis of polyketides and nonribosomal peptides. Such knowledge, in turn, made it possible to produce combinations of PKS and NRPS genes from different microorganisms in order to produce novel antibiotics (McDaniel *et al.*, 1999; Rodriguez and McDaniel, 2001; Pfeifer *et al.*, 2001). Investigating the complete albicidin biosynthesis apparatus is therefore of great interest because such results may contribute to the knowledge as to how PKS and NRPS interact and how they might be manipulated to engineer novel molecules.

15 A second study with *X. albilineans* strain Xa23R1 from Florida revealed that at least two gene clusters, one spanning more than 48 kb, are involved in albicidin production (Rott *et al.*, 1996). This conclusion was based on the following data: (i) fifty Xa23R1 mutants defective in albicidin production were isolated; (ii) a Xa23R1 genomic library of 845 clones, designated pALB1 to pALB845, was constructed; (iii) two overlapping DNA inserts of approximately 47 kb and 41 kb, from clones pALB540 and pALB571 respectively, complemented forty-five mutants and were supposed to contain a major gene cluster involved in albicidin production; (iv) a DNA insert of approximately 36 kb, from clone pALB639, complemented four of the five remaining mutants not complemented by pALB540 and pALB571, and was supposed to contain a second region involved in albicidin production; and (v) the remaining mutant, AM37, which was not complemented by any of the three cosmids pALB540, pALB571 and pALB639, was supposed to be mutated in a third region of the genome involved in albicidin production.

25 30 The DNA sequences of all of the genes required to produce the albicidin family of polyketide antibiotics, the expressed protein amino acid sequences of all of the genes and the deduced structure of Albicidin have not been previously reported, although fragmentary sequences that include three of the biosynthetic genes have been reported. Identification of one albicidin gene, *xabC*, as a methyltransferase gene involved in albicidin biosynthesis is reported

by Huang, G., Zhang, L. & Birch, R.G. (2000a, Gene 255, 327-333) and claimed as biologically active in producing a polyketide antibiotic in PCT WO 02/24736 A1. Identification of a second albicidin gene, *xabA*, as a phosphopantetheinyl transferase gene is reported by Huang, G., Zhang, L. and Birch, R.G. (2000b) Gene 258, 193-199 and claimed as biologically active in producing a polyketide antibiotic in PCT WO 02/24736 A1. Huang, G., Zhang, L. & Birch, R.G. (2001) Microbiology 147, 631-642, report a DNA sequence of *xabB* (GenBank accession # AF239749), a multi functional polyketide-peptide synthetase that may be essential for albicidin biosynthesis in *Xanthomonas albilineans*. This *xabB* gene is reported as full length by Birch in PCT WO 02/24736 A1 (their seq. ID #1) and claimed by Birch in PCT WO 02/24736 A1 as a biologically active polyketide synthase of 4,801 amino acids in length, enabling production of albicidin. However, the DNA sequence reported by Huang et al (2001) in GenBank AF239749 and by Birch in PCT WO 02/24736 A1 (their seq. ID #1) appears to be incomplete and missing 6,234 bp of DNA sequence encoding 2,078 amino acids. We claim the complete DNA sequence of *xabB* (*albI*, our seq. 20) as 20,637 bp, encoding a biologically active polyketide synthase of 6,879 amino acids of in this application (our seq ID #26). Factors affecting biosynthesis by *Xanthomonas albilineans* of albicidins antibiotics and phytotoxins are discussed in J. Appl. Microbiol. 85, 1023-1028. and Wall, M.K. & Birch, R.G. (1997). Genes for albicidin biosynthesis and resistance span at least 69 kb in the genome of *Xanthomonas albilineans*. Lett. Appl. Microbiol. 24, 256-260. A gene from *X. albilineans* strain Xa13, designed AlbF, which confers high level albicidin resistance in *Escherichia coli* and which encodes a putative albicidin efflux pump, was directly submitted to Genbank by Bostock and Birch (Accession n° AF403709).

SUMMARY OF THE INVENTION

The invention provides a novel antibiotic family, Albicidins, produced by three novel biosynthetic gene clusters (XALB1, XALB2, and XALB3) contained within a host cell DNA in which one strand comprises non-contiguously SEQ. ID No. 1, SEQ. ID No. 2 and SEQ ID No. 3, and the cell expresses the DNA to provide peptides including those named AlbI (SEQ ID No. 26) (encoded by SEQ ID No. 20), AlbII (SEQ ID No. 27) (encoded by SEQ ID No. 21), AlbIII (SEQ ID No. 28) (encoded by SEQ ID No. 22), AlbIV (SEQ ID No. 29) (encoded by SEQ ID No. 23), AlbVI (SEQ ID No. 31) (encoded by SEQ ID No. 18), AlbVII (SEQ ID No. 32) (encoded by SEQ ID No. 17), AlbVIII (SEQ ID No. 33) (encoded by SEQ ID No. 16), AlbIX (SEQ ID No. 34) (encoded by SEQ ID No. 15), AlbX (SEQ ID No. 35) (encoded by SEQ ID No. 10), AlbXI (SEQ ID No. 36) (encoded by SEQ ID No. 9), AlbXII (SEQ ID No. 37) (encoded by SEQ ID No. 8), AlbXIII (SEQ ID No. 38) (encoded by SEQ ID No. 7),

AlbXIV (SEQ ID No. 39) (encoded by SEQ ID No. 6), AlbXV (SEQ ID No. 40) (encoded by SEQ ID No. 5), AlbXVII (SEQ ID No. 42) (encoded by SEQ ID No. 11), AlbXVIII (SEQ ID No. 43) (encoded by SEQ ID No. 12), AlbXIX (SEQ ID No. 44) (encoded by SEQ ID No. 13), AlbXX (SEQ ID No. 45) (encoded by SEQ ID No. 14), AlbXXI (SEQ ID No. 46) (encoded by SEQ ID No. 24), and AlbXXII (SEQ ID No. 47) (encoded by SEQ ID No. 25), that in turn interact within the host cell to produce one or more antibiotics as more fully illustrated in Figure 11. In one embodiment the invention comprises a plurality of isolated and purified DNA strands which comprise nucleotide sequences of the group consisting of SEQ ID No: 1 to SEQ. ID No. 25, each individual sequence, except the transposases AlbV (SEQ ID No. 30) (encoded by SEQ ID No. 19) and AlbXVI (SEQ ID No. 41) (encoded by SEQ ID No. 4) found in the XALB1 cluster, being necessary to the biosynthesis of the novel family of antibiotics, Albicidins. The invention also includes the peptides or proteins encoded by the genes of the biosynthetic complex expressed by the combination of DNA with a strand having sequences SEQ ID Nos. 1 to 3. Proteins are named with roman numerals and the prefix Alb from AlbI to Alb XXII have the amino acid sequences of SEQ ID Nos. 26 to 47 (not in Roman numeral order but in the order of placement of the genes within sequences SEQ ID Nos. 1 to 3 that express each protein). Expression of the peptides having the amino acid sequences of SEQ ID Nos. 26 to 29, 31 to 40 and 42 to 47, have been found to be all required for the successful biosynthesis of Albicidins. The invention provides a method for producing Albicidins comprising providing a modified host cell with a heterologous DNA Albicidin Biosynthetic Gene Cluster or set of genes defined as DNA operably comprising DNA sequences substantially similar to SEQ ID Nos. 1 to 3. Substantially the same means DNA having sufficient homology to provide expressed proteins that function to provide an antibiotic material having the structural components identified herein. Preferably a given sequence will have at least 70 percent homology to one of SEQ ID Nos. 1 to 3, preferably 85% homology and most preferably at least 95% homology. The method includes the steps consisting of, modifying the DNA of the host cell to comprise an operable expression system for maintaining the modified host cell under conditions supporting biosynthesis of Albicidins and isolation of Albicidins from the host cell or its environment. The invention further provides a method of production of a group of novel antibiotic materials utilizing at least three of the Sequences selected from the group consisting of DNA SEQ ID No. 1 to SEQ ID No. 25 (excluding transposases encoded by SEQ IDs No. 4 and 19) inclusive in combination with additional sequences to produce a modified Albicidin- like material.

More specifically, the invention provides DNA Sequences comprising at least about 68,498 base pairs more or less and including an about 55,839 bp region from the genome of *X.*

albilineans designated as XALB1 (SEQ ID. No. 1) and additional non contiguous regions having about 2,986 bp, XALB2 (SEQ ID. No. 2), and about 9,673 bp, XALB3 (SEQ ID. No. 3). These sequences were found to be required for biosynthesis of Albicidins. Homology analysis revealed the presence of (i) four large genes with a modular architecture characteristic of polyketide synthases (PKS) and nonribosomal peptide synthetases (NRPS) potentially involved in albicidin precursor biosynthesis; (ii) four smaller genes potentially involved in albicidin substrate biosynthesis (iii) four modifying genes; (iv) one enzyme activating gene, (v) two regulatory genes, (vi) one chaperone gene, (vii) two genes of unknown function; and (viii) two resistance genes. These are named and discussed more fully below. Together these genes allow the successful operation of the biosynthetic pathway when cloned into suitable host cells. Alignment of individual NRPS and PKS domains revealed an extraordinary biosynthetic apparatus believed to involve a *trans*-action of separate PKS and NRPS domains which could contribute to the production of multiple, structurally related albicidins by the same gene cluster. Furthermore, analysis of selectivity-conferring residues indicated that four NRPS modules of XALB1 specify an unusual substrate. Through the interaction of these genes the following methods are enabled:

a) In an alternate embodiment the invention provides a method of producing a polyketide carrying para-aminobenzoic acid and/or carbamoyl benzoic acid by inserting at least one DNA Fragment that encodes a PKS protein into a cell and causing the cell to express the encoded PKS protein under conditions such that the PKS protein functions to produce a polyketide carrying either a para-aminobenzoic acid or a carbamoyl benzoic acid or both. b) Another alternate embodiment is a method of producing polyketide/peptides carrying para-aminobenzoic acid and/or carbamoyl benzoic acid by inserting at least one DNA Fragment that encodes a PKS protein into a cell and causing the cell to express the encoded PKS protein under conditions such that the PKS protein functions to produce a polyketide carrying either a para-aminobenzoic acid or a carbamoyl benzoic acid or both. Or c) In another alternate embodiment the invention provides a method of activating nonproteinogenic amino acids like paraminobenzoic acid and/or carbamoyl benzoic acid for incorporation into peptides or polyketides by inserting at least one DNA Fragment that encodes a PKS protein into a cell and causing the cell to express the encoded PKS protein under conditions such that the PKS protein functions to produce a polyketide carrying either a para-aminobenzoic acid or a carbamoyl benzoic acid or both.

There are three regions of the *X. albilineans* genome specifying albicidin production. The XALB2 and XALB3 regions each contain only one gene, both of which are required for post-translational activation and folding of albicidin PKS and NRPS enzymes. The XALB1, XALB2 and XALB3 gene clusters are characterized by an unusual hybrid NRPS-PKS system, indicating

The invention results from a number of unpredictable results namely the number and complexity of the enzymes involved in biosynthesis. The discovery of the complete sequence required for biosynthesis of Albicidins is previously unreported. The invention provides for a novel process for production of molecule having a polyketide-polypeptide backbone and the formula $C_{40}H_{35}O_{13}N_6$, a molecular weight of 839, and the structural elements shown in Figure 11. The invention further includes (a) the Albicidin Family Biosynthetic Gene Cluster including (b) the structural and regulatory elements of the operons that encode c) the enzymes PKS-1, PKS-2, PKS-3, PKS-4, NRPS-1, NRPS-2, NRPS-3, NRPS-4, NRPS-5, NRPS-6 and NRPS-7 as well as (e) the proteins AlbI to AlbXXII, (f) the isolated enzymes, proteins, and active forms thereof, as well as mutants, fragments, and fusion proteins comprising any of the forgoing; (g) the uses of the enzymes or proteins encoded by the Albicidins Biosynthesis Gene Cluster or any one of its operons, (h) a host cell expressing one or more enzymes or proteins encoded by the Albicidin Family Biosynthetic Gene Cluster; (i) use of host cells having the Albicidins Biosynthesis Gene Cluster to produce an antibiotic; (j) methods of modifying the DNA sequences to produce members of a series of antibiotic compounds having structures related to Albicidins; (k) DNA sequences that encode the same proteins as any of SEQ. ID. Nos. 1 to 25 but differ in specific codons due to the multiplicity of codons that lead to expression of the same amino acid, (l) antibiotics produced by the process of expression of the Albicidin Family Biosynthetic Genes in a genetically modified host cell sustained in a culture medium and thereafter separation of the antibiotic from the host cell and culture medium, (m) an isolated and purified antibiotic produced by a process that includes at least three proteins coded by DNA sequences selected for the group consisting of SEQ. ID Nos. 1 to 25 in combination with additional enzymes that modify the product to provide a non-naturally occurring Albicidins like product having at least one of the useful properties reported for albicidin and (n) a process for producing an antibiotic that comprises modifying a host cell to enhance expression of the DNA of the Albicidin Family

Biosynthetic Gene Cluster by insertion of expression enhancing DNA into the genome of a *Xanthomonas albilineans* strain in a position operative to enhance expression of the enzymes of the Albicidin Family Biosynthetic Gene Cluster, culturing the modified host cell to produce an antibiotic and isolating the antibiotic. The products and methods described above have utility as proteins or as nucleic acids as the case may be, including such uses sources of pyrimidine or purine bases or amino acids, or as animal food supplements and the like, as well as the more important uses to provide antibiotics, plant disease treatment methods, genetically modified disease resistant plants, phytotoxins and the like.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a Physical Map and genetic organization of the DNA Region containing the major gene cluster XALB1 involved in the biosynthesis of Albicidins.

Figure 2 is an illustration of the organization of the four PKS modules and the seven NRPS modules identified in cluster XALB1 and comparison with the organization of the prior art material XabB.

Figure 3 shows the conserved sequence motifs in O-methyltransferases and C-methyltransferases involved in antibiotic biosynthesis in bacteria and in AlbII.

Figure 4 shows the conserved sequence motifs in O-methyltransferases and in different tcmP-like hypothetical proteins and AlbVI.

Figure 5 is an illustration of the alignment of the primary sequences between the conserved motifs A4 and A5 of Alb NPRSs and PKS-4 in *Xanthomonas albilineans* with the corresponding sequences of GrsA (Phe) accession number:P14687 and Blm NRPS-2 (β -Ala) accession number AF210249.

Figure 6 shows Rho-independent transcription terminators identified in the intergenic regions of XALB1 and XALB3 clusters.

Figure 7A shows sequences identified as a putative bidirectional promoter between albX and albXVII in XALB1 for transcriptional control of operons 3 and 4.

Figure 7B shows sequences identified as a putative unidirectional promoter upstream from albXIX for transcriptional control of operon 5 if albXVIII is not expressed.

Figure 8 is a physical map and genetic organization of the DNA region containing the gene clusters XALB2 and XALB3 involved in albicidin production.

Figure 9A is linear model 1 leading to the biosynthesis of only one polyketide-polypeptide albicidin backbone.

Figure 9B is linear model 2 leading to the biosynthesis of four different polyketide-polypeptide

backbone.

Figure 10A is an alignment of the conserved motifs in AT domains from RifA-1, -2, -3, RifB-1, RifE-1 (Rifamycin PKSs, August *et al.*, 1998) and BlmVIII (Bleomycin PKS; Du *et al.*, 2000).

Figure 10B is a comparison of AlbXIII, FenF (a malonyl-CoA transacylase located upstream from *mycA*, Duitman *et al.*, 1999) and LipA (a lipase; Valdez *et al.*, 1999).

Figure 11A is a proposed model for biosynthesis of albicidin, including putative substrates of PKS and NRPS modules.

Figure 11B shows the proposed compositions and structures of albicidins.

10 DETAILED DESCRIPTION OF THE INVENTION

The invention results from the DNA sequencing of the complete major gene cluster XALB1, as well as the noncontiguous fragments XALB2 and XALB3. XALB1 is present in the two overlapping DNA inserts of clones pALB540 and pALB571. Reading frame analysis and homology analyses allow one to predict the genetic organization of XALB1 and to assign a function to the genes potentially required for albicidin production. Based on the alignment of the different PKS and/or NRPS enzymes encoded by XALB1 we proposed a model for the albicidin backbone biosynthesis. However the invention disclosed herein does not depend upon the accuracy of the proposed model. The invention includes the successful cloning and DNA sequencing of the second region of the genome (XALB2) involved in albicidin production and mutated in mutant AM37.

The invention includes the characterization of the third region of the genome (XALB3) involved in albicidin production present in clone pALB639. These results allowed the possibility to characterize all enzymes of the albicidin biosynthesis pathway including structural, resistance and regulatory elements and to engineer overproduction of albicidin.

EXAMPLE 1: Materials and methods

Bacterial strains and plasmids. The source of bacterial strains and their relevant characteristics are described in Table 1.

Media, antibiotics, and culture conditions. *X. albilineans* strains were routinely cultured on modified Wilbrink's (MW) medium at 30°C without benomyl (Rott *et al.*, 1994). For long-term storage, highly turbid distilled water suspensions of *X. albilineans* were supplemented with

glycerol to 15% (vol/vol) and frozen at -80°C . For *X. albilineans*, MW medium was supplemented with the following antibiotics as required at the concentrations indicated: kanamycin, 10 or 25 $\mu\text{g/ml}$; and rifampicin, 50 $\mu\text{g/ml}$. *E. coli* strains were grown on Luria-Bertani (LB) agar or in LB broth at 37°C and were maintained and stored according to standard protocols (Sambrook *et al.*, 1989). For *E. coli*, LB medium was supplemented with the following antibiotics as required at the concentrations indicated: kanamycin, 50 $\mu\text{g/ml}$; ampicillin, 50 $\mu\text{g/ml}$.

Bacterial conjugation. DNA transfer between *E. coli* donor (DH5 α MCR/pAlb389 or pAC389.1, Table 1) and rifampicin-resistant *X. albilineans* recipients (*X.* strains AM10, AM12, AM13, AM36 and AM37, Table 1) was accomplished by triparental conjugation with plasmid pRK2073 as the helper as described previously (Rott *et al.*, 1996).

Table 1 : Bacterial strains and plasmids used in this study

	Relevant characteristics ^a	Reference or source
Strains		
<i>E. coli</i>		
DH5 α	F-f80dlacZAM15 Δ (lacZYA-argF)U169 <i>deoR recA1 endA1</i> <i>hsdR17</i> ($t_k^- m_k^+$) <i>supE44 thi-1 gyrA96 relA1</i>	Gibco-BRL
DH5 α MCR	DH5 α <i>mcrA mcrBC mrr</i>	"
<i>X. albilineans</i>		
Xa23	Wild type from sugarcane (Florida)	Rott <i>et al.</i> , 1996
Xa23R1	Spontaneous Rif ^r derivative of Xa23	"
15 AM strains	Xa23R1::Tn5- <i>gusA</i> , Km ^r , Rif ^r , Tox ^r	"
Plasmids		
PBR325	Tc ^r , Ap ^r , Cm ^r	Gibco-BRL
pBCKS (+)	Cm ^r	Stratagene
pBluescript II	Ap ^r	"
KS (+)		
PRK2073	PRK2013 derivative, Km ^r (<i>npt</i> ::Tn7), Sp ^r , Tra ⁺ , helper plasmid	Leong <i>et al.</i> , 1982
pUFR043	IncW Mob ⁺ LacZ α , Gm ^r , Km ^r , Cos	De Feyter and Gabriel, 1991
pAlb540	47 kb insert from Xa23R1 in pUFR043, Gm ^r , Km ^r	Rott <i>et al.</i> , 1996
pAlb571	36.8 kb insert from Xa23R1 in pUFR043, Gm ^r , Km ^r	"
pAlb639	36 kb insert from Xa23R1 in pUFR043, Gm ^r , Km ^r	"

	pAM15.1	24 kb <i>EcoR</i> I fragment carrying Tn5 and flanking sequences of mutant AM15 in pBR325, Km ^r , Tc ^r , Ap ^r , Cm ^r	"
	pAM40.2	11 kb <i>EcoR</i> I fragment carrying Tn5 and flanking sequences of mutant AM40 in pBR325, Km ^r , Tc ^r , Ap ^r , Cm ^r	"
	pAM45.1	12 kb <i>EcoR</i> I fragment carrying Tn5 and flanking sequences of mutant AM45 in pBR325, Km ^r , Tc ^r , Ap ^r , Cm ^r	"
	pAM12.1	13 kb <i>EcoR</i> I fragment carrying Tn5 and flanking sequences of mutant AM12 in pBR325, Km ^r , Tc ^r , Ap ^r , Cm ^r	"
5	PAM36.2	9 kb <i>EcoR</i> I fragment carrying Tn5 and flanking sequences of mutant AM36 in pBR325, Km ^r , Tc ^r , Ap ^r , Cm ^r	"
	pAlb389	37 kb insert from Xa23R1 in pUFR043, Gm ^r , Km ^r	This study
	pAC389.1	2.9 kb insert from Xa23R1 in pUFR043, Gm ^r , Km ^r	"
	pAlb639A	9.4 kb insert from Xa23R1 in pUFR043, Gm ^r , Km ^r	"
10	PEV639	2.6 kb <i>Sal</i> I insert from Xa23R1 in pUFR043, Gm ^r , Km ^r	"
	pBC/A'	7.5 kb <i>Kpn</i> I fragment carrying a part of fragment A from pAlb571 in pBCKS (+), Cm ^r	"
	pBC/AF	15.2 kb <i>EcoR</i> I fragment carrying fragments A and F from pALB540 in pBCKS (+), Cm ^r	"
	pBC/B	11.0 kb <i>Kpn</i> I fragment B from pAlb571 in pBCKS (+), Cm ^r	"
	pBC/C	6.0 kb <i>Kpn</i> I fragment C from pAlb571 in pBCKS (+), Cm ^r	"
15	pBC/E	2.8 kb <i>Kpn</i> I fragment E from pAlb571 in pBCKS (+), Cm ^r	"
	pBC/F	2.5 kb <i>Kpn</i> I- <i>EcoR</i> I fragment F from pAlb571 in pBCKS (+), Cm ^r	"
	pBC/G	1.9 kb <i>EcoR</i> I fragment G from pAlb571 in pBCKS (+), Cm ^r	"
	pBC/I	1.4 kb <i>Kpn</i> I- <i>EcoR</i> I fragment I from pAlb571 in pBCKS (+), Cm ^r	"
	pBC/J	0.6 kb <i>EcoR</i> I fragment J from pALB540 in pBCKS (+), Cm ^r	"
20	pBC/K	4.7 kb <i>EcoR</i> I fragment K from pALB540 in pBCKS (+), Cm ^r	"
	pBC/L	0.4 kb <i>EcoR</i> I fragment L from pALB540 in pBCKS (+), Cm ^r	"
	pBC/N	7.7 kb <i>EcoR</i> I fragment N from pALB540 in pBCKS (+), Cm ^r	"
	pUFR043/D'	2.2 kb <i>EcoR</i> I- <i>Sau</i> 3A I fragment carrying a part of fragment D from pAlb571 in pUFR043	"
	pAM1	5 kb <i>EcoR</i> I fragment carrying Tn5 and flanking sequences of mutant AM1 in pBluescript II KS (+), Km ^r , Ap ^r	"
	pAM4	12 kb <i>EcoR</i> I fragment carrying Tn5 and flanking sequences of mutant AM4 in pBluescript II KS (+), Km ^r , Ap ^r	"
25	pAM7	6 kb <i>EcoR</i> I fragment carrying Tn5 and flanking sequences of mutant AM7 in pBluescript II KS (+), Km ^r , Ap ^r	"
	pAM10	7 kb <i>EcoR</i> I fragment carrying Tn5 and flanking sequences of	"

	mutant AM10 in pBluescript II KS (+), Km ^r , Ap ^r	
pAM29	10 kb <i>Eco</i> R I fragment carrying Tn5 and flanking sequences of mutant AM29 in pBluescript II KS (+), Km ^r , Ap ^r	"
pAM37	6 kb <i>Eco</i> R I fragment carrying Tn5 and flanking sequences of mutant AM37 in pBR325, Km ^r , Tc ^r , Ap ^r , Cm ^r	"
pAM52	5 kb <i>Eco</i> R I fragment carrying Tn5 and flanking sequences of mutant AM52 in pBluescript II KS (+), Km ^r , Ap ^r	"
DNA Fragment		
PR37	1.1 kb <i>Hind</i> III- <i>Hind</i> III from pAM37	"

* Ap^r, Cm^r, Gm^r, Km^r, Rif^r, Sp^r, Tc^r: resistant to ampicillin, chloramphenicol, gentamycin, kanamycin, rifampicin, spectinomycin, tetracycline, respectively. Tox⁻, deficient in albicidin production. Tn5-*gusA*, Tn5-*uidA1* Km^r Tc^r, forms transcriptional fusions.

Assay of albicidin production. Albicidin production was tested by a microbiological assay as described previously (Rott *et al.*, 1996). Rifampicin and kanamycin exconjugants were spotted with sterile toothpicks (2-mm-diameter spots) onto plates of SPA medium (2% sucrose, 0.5% peptone, 1.5% agar) and incubated at 28°C for 2-5 days. The plates were then overlaid with a mixture of *E. coli* DH5α (10⁷ cells in 2 ml of distilled water) plus 2 ml of molten 1.5% (wt/vol) Noble agar (Difco) at ca. 65°C and examined for inhibition zones after 24 h at 37°C.

Nucleic acid manipulations. Standard molecular techniques were used to manipulate DNA (Sambrook *et al.*, 1989) except for total genomic DNA preparation. Total genomic DNA for southern blot hybridization was prepared as described by Gabriel and De Feyter (1992).

PCR Conditions. PCR amplifications were performed in an automated thermal cycler PTC-100™ (MJ Research, Inc). The 25 µl PCR reaction mix consisted of 100 ng of genomic DNA or 1 ng of plasmid DNA, 2.5 µl of 10X PCR buffer without MgCl₂ (Eurobio), 80 µM dNTP mix, 2.5 units of EUROBIOTAQII® (Eurobio), 25 pmoles of each primer, 2.0 mM MgCl₂ (Eurobio) and sterilized distilled water to final volume. The PCR program was 95°C for 2 min, 25 cycles at 94°C for 1 min, T_m for 1 min and 72°C for 1 min, with a final 72°C extension for 5 min. T_m temperature was determined for each couple of primers and varied between 55°C and 60°C. A 5 µl aliquot of each amplified product was analyzed by electrophoresis through a 1% agarose gel. For sequencing, PCR products were cloned with the pGEM®-T Easy Vector System (Promega).

Oligonucleotide synthesis. Oligonucleotides were purchased from Genome Express (Grenoble or Montreuil, France).

5 **DNA sequencing.** Automated DNA sequencing was carried out on double-stranded DNA by the dideoxynucleotide chain termination (Sanger *et al.*, 1977) using a Dye Terminator Cycle Sequencing kit and an ABI Perkin-Elmer sequencer according to the manufacturer's procedure. Both DNA strands were sequenced with universal primers or with internal primers (20mers). This service was provided by Genome Express (Grenoble, France). Computer-aided sequence analyses were carried out using Sequence Navigator™ (Applied Biosystems, Inc) and SeqMan
10 (DNASTAR Inc.) programs.

Sequence analysis. Nucleotide sequences were translated in all six reading frames using EditSeq (DNASTAR Inc.). Potential products of ORFs longer than 100 b were compared to protein data bases by the PSI-BLAST program (Swiss-Prot and Genbank) on the NCBI site
15 (<http://www.ncbi.nlm.nih.gov/>) using Altschul program (Altschul *et al.*, 1997). The TERMINATOR program of the Genetics Computer Group was used to identify putative Rho-independent transcription terminators.

20 Procedures

EXAMPLE 2: Sequencing of the double strand region of 55,839 bp from *X. albilineans* containing XALB1 SEQ ID NO. 1

In Figure 1 is presented a physical map and genetic organization of XALB1. In the figure, E and K are restriction endonuclease sites for *EcoRI* and *KpnI*, respectively. Rectangular
25 boxes represent DNA fragments labeled A through N. The numbers below each rectangular box are the number of Tn5-*gus* insertion sites previously located in each DNA fragment (Rott *et al.*, 1996). The DNA inserts carried by plasmids pALB571 and pALB540 are represented by bold bars above the physical map. The location and direction of putative orfs identified in the XALB1 gene cluster are shown by arrows. Precise positions and proposed functions for individual orfs
30 are summarized in tables 2 and 3, respectively. Position of insertional sites of eight albicidin-defective mutants determined by sequencing are indicated by vertical arrows. The location and direction of putative ORFS identified in the XALB1 gene cluster are shown by arrow shapes. These twenty putative ORFs are potentially organized in four or five operons, as

indicated at the bottom of the figure. Patterns indicate NRPS and PKS genes (diagonal crosshatch), methyl transferase and esterase genes (hollow rectangles), carbamoyl transferase gene (fine crosshatch), benzoate-derived products biosynthesis genes (white), regulatory genes (vertical lined), resistance genes (diagonal lines) and other genes with function of unknown significance to albicidin production (black), and three insertional sites of eight albicidin-defective mutants determined by sequencing are indicated by vertical arrows. Dotted regions in the physical map and in ORFs represent the two internal duplicated DNA regions of XALB1.

The sequence illustrated in Figure 1 was generated as follows. The sources of DNA are set out in Table 1. DNA fragments F, E, B, C, I, and G, generated by the digestion of cosmid pALB571 (Rott *et al.*, 1996) with *Eco*RI and/or *Kpn*I, were subcloned into pBCKS (+) and were sequenced from the resulting subclones, pBC/F, pBC/E, pBC/B, pBC/C, pBC/I and pBC/G. DNA fragment D' which corresponds to the part of fragment D present in cosmid pALB571 was sequenced from plasmid pUFR043/D' obtained following self ligation of the complete *Eco*RI digested cosmid pALB571. DNA fragment H was sequenced from pAM45.1 (Rott *et al.*, 1996), obtained following cloning into vector pBR325 of the 12kb *Eco*RI fragment carrying Tn5 and flanking sequences from mutant strain XaAM45. DNA fragment A' contains the part of fragment A present in cosmid pALB571 and was subcloned into vector pBCKS (+) and the resulting plasmid pBC/A' was used for sequencing. The presence of a large internal duplication made alignment of sequence data obtained from pBC/A' difficult. This difficulty was resolved using sequence data obtained from an additional plasmid, pAM4, obtained following cloning into vector pBluescript II KS (+) of the 12kb *Eco*RI fragment carrying Tn5 and flanking sequences from mutant strain XaAM4, which contains only one copy of the large internal duplication. Sequence data from pBC/A' were used to determine the first 1542 bp of fragment A' between nucleotides C-19001 and G-20543. Sequence data from pAM4 and pBC/A' were used to determine the last 4823bp of fragment A' between nucleotides G-21653 and G-26477. The overlapping region between nucleotides G-20469 and C-22159 was amplified by PCR from cosmid pALB571 using primers contig13-1160 (5'gcgtagcgtgtgtccagtagg3') SEQ ID NO. 48 and pAM4-14 (5'gctggaacccgagaatctga3') SEQ ID NO. 49, and was sequenced. Resulting sequence data were used to complete

sequencing of DNA fragment A'. The junctions A/F, F/H, H/E, E/B, B/C, C/I, I/G, G/D between corresponding DNA fragments were sequenced directly from cosmid pALB571. EcoRI DNA fragment containing fragments A and F was subcloned from pALB540 into pBCKS (+), and the resulting plasmid pBC/AF was used to determine the part of DNA fragment A which was not present in cosmid pALB571 between nucleotides G-13682 and G-19001. EcoRI DNA fragments J, K, L, N were subcloned from pALB540 into pBCKS (+) and were sequenced from resulting plasmid pBC/J, pBC/K, pBC/L, and pBC/N. The junctions L/K, K/J and J/A between corresponding DNA fragments were sequenced directly from cosmid pALB540. DNA region between nucleotides G-7517 and T-8721 was amplified by PCR from cosmid pALB540 using primers E114 (5'gacacgatcagccgctagga3') SEQ ID NO. 50 and EI4-380 (5'accagcagttgggccagcct3') SEQ ID NO. 51 and was sequenced. Resulting sequence data were used to determine the sequence of fragment M and of junctions N/M and M/L. The nucleotide sequence of 55,839 bp containing the entire major gene cluster involved in Albicidin production was sequenced on both strands.

EXAMPLE 3: Analysis of the large internal duplications in the DNA sequence of XALB1

The sequence of the 55,839 bp genomic region (SEQ ID NO. 1) contains two large internal duplications as shown by the dotted regions in the physical map of Figure 1. A direct duplication of 1736 bp was located in DNA fragment A between nucleotides G-19904 and G-21639 and between nucleotides G-23057 and G-24792. Another direct duplication of a 2727 bp was found in DNA fragments B and C between nucleotides C-40410 and G-43136 and between nucleotides C-46644 and G-49370. Comparison of the two copies of each duplication revealed that the two copies of the 1736 bp duplication are identical except for one nucleotide at position 21058, and that the two copies of the 2727 bp duplication are 98.8% identical and differ by 30 nucleotides.

EXAMPLE 4: Comparison of XALB1 with the *xabB* EcoRI fragment

Comparison of the DNA sequence of the 55,839 bp genomic region described in this study with the partial DNA sequence of 16,511 bp of the same region in Huang et al.,

2001 (described by Huang et al. as an *EcoRI* fragment including full length *xabB* from *X. albilineans* strain Xa13 [GenBank accession N° AF239749]), revealed that the DNA sequence from strain Xa13 over 16,511 bp is identical to the sequence from strain Xa23R1, described herein, with the following exceptions: 1) five nucleotides are different at positions 42963, 42972, 42980, 43014 and 43071 of the XALB1 sequence, and 2) nucleotides from positions 43137 to 49370 are missing (internal to *albI*; refer Fig. 1). Analysis of genomic DNA of seven strains isolated from different countries (Australia, Reunion Island, Kenya, Zimbabwe and USA), digested by *KpnI* and hybridized with the pBC/C plasmid (Table 1) labeled with ³²P, revealed that two DNA fragments corresponding to the XALB1 fragments B and C were present in all strains (data not shown). This result indicated that all studied strains contain *albI* and not *xabB* because in *albI* the pBC/C plasmid probe hybridizes with the large internal duplication present in both DNA fragments B and C (Figure 1). Based on this observation we postulated that the DNA sequence of XabB reported as full length by Birch in PCT WO 02/24736 A1 (Their seq. ID#1) appears to be incomplete and missing 6,234 bp of DNA sequence encoding 2,078 amino acids.

EXAMPLE 5: Reading frame analysis in XALB1

Analysis of the 55,839 bp double strand region for coding sequences revealed the presence of 20 open reading frames (ORFs) designated *albI* to *albXX* (Table 2 below) which are distributed in four groups of genes according to their position and their orientation in the XALB1 cluster (Figure 1). Genes of each group may form part of the same operon as judged by their overlapping stop and start codons, or by the relatively short intergenic region which varies from 5 to 274 nucleotides. The 20 ORFs appear to be organized in four operons: operon 1 formed by *albI* - *albIV*; operon 2 by *albV* - *albIX*; operon 3 by *albX* - *albXVI*; operon 4 by *albXVII* - *albXX*. The majority of *alb* ORFs are initiated with an ATG codon, except *albI* and *albXVII* which are initiated with a TTG codon, and *albIV* and *albVI* which are initiated with a GTG start codon. In seven ORFs of XALB1, start codons are preceded by the consensus sequence GAGG which may correspond to the ribosome binding site. Other ORFs are preceded by a less conserved sequence which contain at least three nucleotides A or G and which may serve as a weak

ribosome binding site.

EXAMPLE 6: Sequencing of the Tn5 insertional site of eight *tox*⁻ mutants previously located in XALB1

5 Eight of the 45 *X. albilineans* *Tox*⁻ mutants complemented by cosmid pALB540 and/or cosmid pALB571 and previously described (Rott *et al.*, 1996) were further analyzed. All eight mutants contain a single Tn5 insertion and correspond to the following *X. albilineans* strains: XaAM7, XaAM15, XaAM45, and XaAM52 which are complemented by pALB571 but not by pALB540; XaAM4, XaAM29 and XaAM40
10 which are complemented by both cosmids; and XaAM1 which is complemented by pALB540 but not by pALB571. The Tn5 insertional site of each *Tox*⁻ mutant was sequenced from plasmids obtained following cloning in pBR325 or in pBluescript II KS (+) of the EcoRI fragments carrying Tn5 and flanking sequence using the sequencing primer GUSN (5'tgcccacaggccgtcgagt3') SEQ ID No. 52 that annealed 135 bp
15 downstream from the insertional sequence IS50L of Tn5-*gusA*. The sequence of the Tn5 insertional site was compared with the 55,839 bp sequence containing XALB1 in order to determine the *alb* gene disrupted in each *Tox*⁻ mutant. *albI* is disrupted by the Tn5 insertion in XaAM15 and XaAM45 at position 33443 and 34229, respectively (Figure 1). *albIV* is disrupted by the Tn5 insertion in XaAM7 and XaAM52 at position 53704 and
20 53915, respectively. *albIX* is disrupted by the Tn5 insertion in XaAM4, XaAM29 and XaAM40 at position 21653, 23444 and 24376, respectively. *albXI* is disrupted by the Tn5 insertion in XaAM1 at position 13301. These results are in accordance with the previous characterization of *Tox*⁻ mutants using Southern blot hybridization (Rott *et al.*, 1996), except for XaAM1. The Tn5-*gusA* insertion site of XaAM1 was previously located in
25 DNA fragment A (Rott *et al.*, 1996) but results of this study showed that this site is located in DNA fragment J (Figure 1).

Table 2: Analysis of putative translational signals and location of all putative orfs identified in the XALB1 gene cluster

	Intergenic spacing between consecutive orfs in each putative operon	Orf	Potential RBS ^a (distance from start codon)	Start codon (position)	Stop codon (position)
5	Operon 1 (strand +)				
		<i>albI</i>	GAGGG (5 b)	TTG (30166)	TAG (50805)
	45 b	<i>albII</i>	GAGGG (5 b)	ATG (50851)	TAA (51882)
	ATG overlaps TAA	<i>albIII</i>	GAGGG (7 b)	ATG (51882)	TGA (52385)
10	GTG overlaps TGA	<i>albIV</i>	GAGG (7 b)	GTG (52382)	TAA (55207)
	Operon 2 (strand -)				
		<i>albV</i>	GGAGG (8 b)	ATG (29929)	TAA (29210)
	87 b	<i>albVI</i>	AAGG (4 b)	GTG (29122)	TGA (28262)
	61 b	<i>albVII</i>	GAG (4 b)	ATG (28200)	TAG (25903)
15	7 b	<i>albVIII</i>	AGGTG (4 b)	ATG (25895)	TAA (24903)
	20 b	<i>albIX</i>	GGTG (3 b)	ATG (24882)	TGA (19003)
	Operon 3 (strand -)				
		<i>albX</i>	GGGGG (8 b)	ATG (14497)	TGA (14246)
20	81 b	<i>albXI</i>	AGGAAA (6 b)	ATG (14164)	TGA (13217)
	5 b	<i>albXII</i>	GGCCTGA (5 b)	ATG (13211)	TAA (11856)
	36 b	<i>albXIII</i>	GGGG (3 b)	ATG (11819)	TAA' (10866)

	12 b	<i>albXIV</i>	GGAG (8 b)	ATG (10853)	TAG (9363)
	41 b	<i>albXV</i>	GGAA (6 b)	ATG (9321)	TAG (7567)
	208 b	<i>albXVI</i>	GGAGG (4 b)	ATG (7358)	TAG (7092)
5	Operon 4 (strand +)				
		<i>albXVII</i>	GGGAGG (5 b)	TTG (14909)	TGA (17059)
	274 b	<i>albXVIII</i>	GCTCAG (8 b)	ATG (17334)	TGA (17747)
	Overlap (17 b)	<i>albXIX</i>	AGG (9 b)	ATG (17728)	TGA (18330)
	41 b	<i>albXX</i>	GCAA (8 b)	ATG (18372)	TAG 18980)
10					

^a: Ribosomal Binding Site

EXAMPLE 7: Homology analysis of proteins potentially encoded by XALB1

Preliminary functional assignments of individual ORFs were made by comparison of the deduced gene products with proteins of known functions in the Genbank database. The results are set out in Table 3 below. Among the ORFs identified from the sequenced XALB1 gene cluster, we found (i) four genes, *albI* SEQ ID No. 20, *albIV* SEQ ID No. 23, *albVII* SEQ ID No. 17 and *albIX* SEQ ID No. 15, encoding PKS and/or NRPS modules; (ii) one carbamoyl transferase gene, *albXV* SEQ ID No. 5; (iii) two esterase genes, *albXI* SEQ ID No. 9 and *albXIII* SEQ ID No. 7; (iv) two methyltransferase genes, *albII* SEQ ID No. 21 and *albVI* SEQ ID No. 18; (v) two benzoate-derived products biosynthesis genes, *albXVII* SEQ ID No. 11 and *albXX* SEQ ID No.14; (vi) two putative albicidin biosynthesis regulatory genes, *albIII* SEQ ID No. 22 and *albVIII* SEQ ID No. 16; (vii) two putative albicidin resistance genes, *albXIV* SEQ ID No. 6 and *albXIX* SEQ ID No. 13; and (viii) two additional ORFs encoding proteins similar to transposition proteins, *albV* SEQ ID No. 19 and *albXVI* SEQ ID No. 4. No known function was found in the database for *albX* SEQ ID No. 10 and *albXII* SEQ ID No. 8. The potential product of *albXVIII* SEQ ID No. 12

appeared to be a truncation of an enzyme with strong similarity to 4-amino-4-deoxychorismate lyase and branched-chain amino acid aminotransferase. Since the gene encoding the predicted product is roughly half the length of other such lyase or aminotransferase genes, *albXVIII* may be the result of a recombination event and may be non functional.

Table 3: Deduced functions of the ORFs in the major albicidin biosynthetic cluster X-ALB1

Orf	Number of amino acids	Sequence homolog	Proposed function
Operon 1			
<i>albI</i>	6879	XabB (AAK15074)	Polyketide- peptide synthase <u>PKS modules</u> <u>PKS domains</u> PKS-1 AL ACP1 PKS-2 KS1 KR ACP2 ACP3 PKS-3 KS2 PCP1 <u>NRPS modules</u> <u>NRPS domains</u> NRPS-1 C A PCP2 NRPS-2 C <u>A</u> PCP3 NRPS-3 C A PCP4 NRPS-4 C
<i>albII</i>	343	XabC (AAK15075)	C-methyltransferase
<i>albIII</i>	167	ComAB (CAA71583)	Activator of <i>alb</i> genes transcription
<i>albIV</i>	941	MycA (T44806) WbpG (E83253)	Peptide synthase <u>NRPS module</u> <u>NRPS domains</u> NRPS-5 A PCP5
Operon 2			
<i>albV</i>	239	Thp (AAK15074)	No function (transposition)
<i>albVI</i>	286	TcmP (AAA67510)	O-methyltransferase
<i>albVII</i>	765	HbaA (A58538)	4-hydroxybenzoate CoA ligase
<i>albVIII</i>	330	SyrP (AAB63253)	Regulation
<i>albIX</i>	1959	DhbF (CAB04779)	Peptide synthase <u>NRPS modules</u> <u>NRPS domains</u>

			NRPS-6 NRPS-7	A C	PCP6 A	PCP7
Operon 3						
<i>albX</i>	83	MbtH (O05821)	Unknown			
<i>albXI</i>	315	SyrC (U25130)	Thioesterase			
<i>albXII</i>	451	BoxB (AAK006000.1)	Unknown			
<i>albXIII</i>	317	hp ^d (AAK25001)	Esterase			
<i>albXIV</i>	496	ActII-2 (p46105)	Albicidin transporter			
<i>albXV</i>	584	hp ^d (08390)	Carbamoyl transferase			
<i>AlbXVI</i>	88	OrfA (AAC03166)	No function (transposition)			
Operon 4						
<i>albXVII</i>	716	PabAB (CAC22117)	Para-amino benzoate synthase			
Operon 5						
<i>albXVIII</i>	137	ADCL (AAG06352)	No function (not functional)			
<i>albXIX</i>	200	McbG (P05530)	Immunity against albicidin			
<i>albXX</i>	202	UbiC (S25660)	4-hydroxybenzoate synthetase			

^aProtein accession numbers in Genbank are given in parentheses.

^bNRPS and PKS domains are abbreviated as follows: A, adenylation; ACP, acyl carrier protein, AL, acyl CoA ligase; C, condensation; KR, ketoreductase; KS, ketoacyl synthase; PCP, peptidyl carrier protein

^cUnderlined domains are likely inactive due to the lack of highly conserved motifs.

^dhypothetical protein

EXAMPLE 8: The *alb* PKS and/or NRPS genes

The potential product of *albI*, designated AlBI SEQ ID No. 20, is a protein of 6879 aa with a predicted size of 755.9 kDa. This protein is very similar to the potential product of the *xabB* gene from *X. albilineans* strain Xa13 from Australia (Huang *et al.*, 2001), but it differs in length and size (See Table 4 below). XabB is a protein of 4801 aa with a predicted size of 525.7 kDa. Comparison of AlBI with XabB revealed that the N-terminal regions from Met-1 to Ile-4325 of both proteins are identical except for five amino-acids which are Tyr-3941, Pro-3952, Ala-4054, Ala-4271 and Gln-4284 in AlBI and His-3941, Ala-3952, Val-4054, Val-4271 and Glu-4284 in XabB. The same comparison revealed that the AlBI C-terminal region from Arg-6404 to the stop codon is 100% identical to the XabB C-terminal region from Arg-4326 to the stop codon.

The N-terminal region (from Met-1 to Asp-3235) of AlbI is 100% identical to the corresponding region in XabB which was previously described as similar to many microbial modular PKS (Huang *et al.*, 2001). This PKS region may be divided into three modules (Figure 2). Abbreviations used in the Figure are: A, adenylation; ACP, acyl carrier protein; 5 AL, acyl-CoA ligase; C, condensation; KR, β -ketoacyl reductase; KS, β -ketoacyl synthase; NRPS, nonribosomal peptide synthase; PCP, peptidyl carrier protein; PKS, polyketide synthase; TE, thioesterase; HBCL, 4-hydroxybenzoate-CoA ligase. The question mark in the NRPS-2 domain indicates that this A domain is incomplete. The first module designated PKS-1 contains acyl-CoA ligase (AL) and acyl carrier protein (ACP1) domains. The second 10 module designated PKS-2 contains β -ketoacyl synthase (KS1) and β -ketoacyl reductase (KR) domains followed by two consecutive ACP domains (ACP2 and ACP3). The third module designated PKS-3 contains a KS domain (KS2) followed by a PCP domain (PCP1). Apart their very high similarity with XabB, these three PKS modules exhibited the highest degree of overall similarity with polyketide synthases SafB and PksM from *Myxococcus xanthus* and 15 *Bacillus subtilis*, respectively (Table 4). The motifs characteristic of these domains are 100% identical to those of XabB which were previously aligned with those from other organisms (Huang *et al.*, 2001). The AL domain contains the conserved adenylation core sequence (SGSSG) and the ATPase motif (TGD). The three ACP domains contain a 4'-phosphopantetheinyl-binding cofactor box GxDS(IL), except that A replaced G in ACP1. 20 Both KS domains contain motif GPxxxxxxCSxSL around the active site Cys, and two His residues downstream from the active site Cys, in motifs characteristic of these enzymes. The KR domain contains the NAD(P)H-binding site GGxGxLG.

The PKS part of AlbI is linked by the PCP1 domain to the four apparent nonribosomal peptide synthase modules designated NRPS-1, NRPS-2, NRPS-3 and NRPS-4 (Figure 2). 25 NRPS-1, NRPS-2 and NRPS-3 modules display the ordered condensation, adenylation (A) and PCP domains typical of such enzymes (Marahiel *et al.*, 1997), and NRPS-4 consists of an extra C domain which may correspond to an incomplete NRPS module. Known conserved sequences, characteristic of the domains commonly found in peptide synthases (Marahiel *et al.*, 1997), were compared to those from NRPS-1, NRPS-2, NRPS-3 and NRPS-4 (Tables 5, 6 30 and 7). Sequences characteristic of C, A, or PCP domains are conserved in these four NRPS, except in A domain of NRPS-2 module, suggesting that this latter A domain may be not functional. Comparison of the four NRPS modules among themselves revealed that NRPS-2, NRPS-3 and NRPS-4 modules were 30.7%, 94.4% and 47.5% similar to NRPS-1 module, respectively. Comparison with XabB revealed NRPS-2 and NRPS-3 modules were not present

in XabB which contains only NRPS-1 and NRPS-4 modules (Figure 2). The dotted box in Figure 2 corresponds to the apparent deletion of the NRPS-2 and NRPS-3 modules in XabB as compared to AlbI. Apart their very high similarity with XabB, Alb I NRPS modules exhibited the highest degree of overall similarity with non-ribosomal peptide synthases NosA and NosC from *Nostoc* sp..

albIV potentially encodes a protein of 941 aa (AlbIV) with a predicted size of 104.8 kDa. AlbIV is similar to several non-ribosomal peptide synthases such as the BA3 peptide synthase involved in bacitracin biosynthesis in *Bacillus licheniformis* (Table 4). AlbIV forms one NRPS module designated NRPS-5 that contains only an A domain and a PCP domain (Figure 2). Sequences characteristic of the domains A and PCP commonly found in peptide synthases (Marahiel *et al.*, 1997) are conserved in AlbIV (Tables 6 and 7). However the A domain present in AlbIV differs from A domains commonly found in peptide synthases: conserved sequences corresponding to cores A8 and A9 in AlbIV are separated by a very long peptide sequence of 390 amino-acids. This additional peptide sequence exhibits a significant similarity with the protein WbpG of 377 amino acids involved in the biosynthesis of a lipopolysaccharide in *Pseudomonas aeruginosa* (Table 4).

albVII potentially encodes a protein of 765 aa (AlbVII) with a predicted size of 83.0 kDa similar to the 4-hydroxybenzoate-CoA ligase from several bacteria and the closest protein (HbaA) was from *Rhodopseudomonas palustris* (Table 4). High similarity between AlbVII and HbaA suggests that AlbVII is a 4-hydroxybenzoate-CoA ligase and constitutes a fourth PKS module designed PKS-4. The size of HbaA is smaller (539 aa) and the similarity between the two proteins starts only at the residue 277 of AlbVII and at the residue 28 of HbaA. Comparison of AlbVII sequence located upstream from residue 277 produced no significant alignment. AlbVII, like 4-hydroxybenzoate-CoA ligases, contains some conserved sequences characteristic of the A domain commonly found in peptide synthases (Table 6).

albIX potentially encodes a protein of 1959 aa (AlbIX) with a predicted size of 218.4 kDa similar to non-ribosomal peptide synthases. Known conserved sequences, characteristic of the domains commonly found in peptide synthases (Marahiel *et al.*, 1997), were compared with those from AlbIX which forms two NRPS modules designated NRPS-6 and NRPS-7 (Tables 5, 6 and 7). NRPS-6 contains only one A and one PCP domain. NRPS-7 contains the three domains characteristic of NRPS modules (A-C-PCP) followed by a TE domain (Figure 2). Apart their very high similarity with XabB, NRPS-6 and NRPS-7 modules exhibited the highest degree of overall similarity and identity with non-ribosomal peptide synthases Dhbf from *B. subtilis* and NosA from *Nostoc* sp. (Table 4).

Table 4 : Summary of results obtained from BLAST analyses.

Putative Alb protein	No. of aa residues	Protein homolog	Origin	Genbank accession #	Score	Expect	Identities	Positives	Gaps
AlbI	6879								
PKS-1		XabB (4801 aa) SafB (1770 aa)	<i>Xanthomonas albilineans</i> <i>Mycococcus xanthus</i>	AAK15074 AAC44128	1352 bits (3498) 231 bits (589)	0.0 2e-59	730/730 (100%) 175/532 (32%)	730/730 (100%) 269/532 (49%)	23/532 (4%)
PKS-2		XabB (4801 aa) PksM (4273 aa)	<i>X. albilineans</i> <i>Bacillus subtilis</i>	AAK15074 CAB13603	3464 bits (8983) 887 bits (2292)	0.0 0.0	1882/1882 (100%) 626/1896 (33%)	1882/1882 (100%) 938/1896 (49%)	140/1896 7%
PKS-3		XabB (4801 aa) PksM (4273 aa)	<i>X. albilineans</i> <i>B. subtilis</i>	AAK15074 CAB13603	1274 bits (3296) 577 bits (1486)	0.0 e-163	653/653 (100%) 293/584 (50%)	653/653 (100%) 391/584 (66%)	17/584 (2%)
NRPS-1		XabB (4801 aa) NosA (4379 aa)	<i>X. albilineans</i> <i>Nostoc</i> sp	AAK15074 AF204805	1934 bits (5010) 618 bits (1594)	0.0 e-176	1035/1046 (99%) 398/1104 (36%)	1039/1046 (99%) 586/1104 (53%)	86/1104 (7%)
NRPS-2		NosA (4379 aa) Peptide synthase (5060 aa)	<i>Nostoc</i> sp <i>Anabaena</i> sp	AF204805 CAC01604	416 bits (1069) 402 bits (1034)	e-115 e-111	337/1127 (29%) 315/1073 (29%)	496/1127 (43%) 479/1073 (44%)	114/1073 (10%)
NRPS-3		XabB (4801 aa) NosA (4379 aa)	<i>X. albilineans</i> <i>Nostoc</i> sp.	AAK15074 AF204805	1847 bits (4784) 610 bits (1573)	0.0 e-173	997/1044 (95%) 392/1069 (36%)	1007/1044 (96%) 571/1069 (52%)	86/1069 (8%)

NRPS-4		XabB (4801 aa) NosC (3317 aa)	<i>X. albilineans</i> <i>Nostoc sp</i>	AAK15074 AAF17280	889 bits (2297) 240 bits (613)	0.0 2e-62	468/468 (100%) 156/438 (35%)	468/468 (100%) 229/438 (51%)	20/438 (4%)
AlbII	343	XabC (343 aa) MrmMII (326 aa) TcmO (339 aa)	<i>X. albilineans</i> <i>Streptomyces argillaceus</i> <i>S. glaucescens</i>	AAK15075 AAD55584 P39896	633 bits (1633) 144 bits (361) 81.7 bits (199)	0.0 1e-34 1e-14	343/343 (100%) 98/323 (30%) 79/314 (25%)	343/343 (100%) 154/323 (47%) 140/314 (44%)	4/323 (1%) 12/314 (3%)
AlbIII	167	comA operon protein 2 (136 aa) ComAB (116 aa)	<i>E. coli</i> <i>Bacillus licheniformis</i>	AAC74756 CAA71583	133 bits (335) 97.6 bits (242)	1e-30 8e-20	68/135 (50%) 53/111 (47%)	89/135 (65%) 68/111 (60%)	1/111 (0%)
AlbIV	941								
PKS-4		BA3 (6359 aa) WbpG (377 aa)	<i>B. licheniformis</i> <i>Pseudomonas aeruginosa</i>	AAC06348 E83253	361 bits (926) 81.6 bits (200)	2e-98 4e-15	190/441 (43%) 44/119 (36%)	267/441 (60%) 70/119 (57%)	14/441 (3%) 4/119 (3%)
AlbV	239	Thp (240 aa) IS transposase (260 aa)	<i>X. albilineans</i> <i>Yersinia pestis</i>	nd AAC82714	nd 160 bits (404)	0.0 1e-38	240/240 (100%) 87/183 (47%)	240/240 (100%) 122/183 (66%)	2/183 (1%)

AlbVI	286	Hypothetical protein TcmP (276 aa)	<i>Mycobacterium tuberculosis</i> <i>Pasteurella multocida</i> Rhodospseudomonas palustris	AAK46042 AAK03406	138 bits (347) 36.6 bits (83)	6e-32 0.24	92/224 (41%) 32/132 (28%)	125/224 (55%) 65/132 (49%)	18/224 (8%) 29/197 (6%)
AlbVII	765	4-hydroxybenzoate- CoA ligase (539 aa)	<i>S. verticillus</i> Pseudomonas syringae	AAA62604 AF210249 AAB63253	203 bits (513) 245 bits (619) 182 bits (458)	5e-51 6e-64 5e-45	156/492 (31%) 130/309 (42%) 106/306 (34%)	242/492 (48%) 182/309 (58%) 155/306 (50%)	31/492 (6%) 2/309 (0%) 4/306 (1%)
AlbIX	1959								

NRPS-6	XabB (4801 aa) DhbF (1278 aa)	<i>X. albilineans</i> <i>B. subtilis</i>	AAK15074 CAB15186	481 bits (1239) 354 bits (908)	e-135 1e-96	286/608 (47%) 222/608 (36%)	374/608 (61%) 341/608 (55%)	23/208 (3%) 21/608 (3%)
NRPS-7	XabB (4801 aa) NosA (4379 aa)	<i>X. albilineans</i> <i>Nostoc</i> sp.	AAK15074 AF204805	874 bits (2258) 551 bits (1420)	0.0 e-155	515/1110 (46%) 388/1148 (33%)	682/1110 (61%) 583/1148 (49%)	52/1110 (4%) 84/1148 (7%)
AlbX	Hypothetical protein (72 aa) MbtH (71 aa)	<i>P. aeruginosa</i> <i>M. tuberculosis</i>	AAG05800 CAB08480	75.6 bits (185) 59 bits (142)	1e-13 9e-09	34/61 (55%) 25/55 (45%)	44/61 (71%) 37/55 (66%)	- -
AlbXI	SyrC (433 aa) Hydrolase (261 aa)	<i>P. syringae</i> <i>S. coelicolor</i>	AA85161 CAA16200	34.4 bits (78) 34 bits (77)	1.9 2.9	23/93 (24%) 19/60 (31%)	40/93 (42%) 30/60 (49%)	- -
AlbXII	BoxB (473 aa)	<i>Azoarcus evansii</i>	AAK00599	293 bits (751)	3e-78	174/448 (38%)	243/448 (53%)	12/448 (2%)
AlbXIII	Hypothetical protein (335 aa) Plasma PAF acetylhydrolase (444 aa)	<i>Caulobacter crescentus</i> <i>Canis familiaris</i>	AAK25001 AAC48484	99.5 bits (247) 37.5 bits (86)	5e-200	88/296 (29%) 43/156	125/296 (41%) 56/156	5/296 (1%) 44/156 (28%)
AlbXIV	Putative transmembrane efflux protein (505 aa) AlbF, putative albicidin efflux pump (496 aa)	<i>S. coelicolor</i> <i>X. albilineans</i>	CAB90983 AF403709	225 bits (574) 736 bits (1900)	0	154/465 (33%) 496/496 (100%)	240/465 (51%) 496/496 (100%)	8/465 (1%) -
AlbXV	Probable carbamoyl transferase (585 aa) BlmD (545 aa)	<i>P. aeruginosa</i> <i>S. verticillius</i>	AAG08390 AAG02370	201 bits (513) 192 bits (506)	1e-50 1e-47	158/458 (34%) 149/441 (33%)	222/458 (47%) 209/441 (46%)	39/458 (8%) 33/441 (7%)

AlbXVI	88	Transposase (363 aa) Transposase OrfA (88 aa)	<i>X. axonopodis</i> <i>Desulfovibrio vulgaris</i>	AF263433 AAC03166	64.8 bits (157) 61.0 bits (147)	2e-10 3e-09	27/45 (60%) 29/54 (53%)	40/45 (88%) 38/54 (69%)	- -
AlbXVII	716	Para-aminobenzoate synthase (723 aa)	<i>Streptomyces griseus</i>	CAC22117	503 bits (1295)	e-141	302/699 (43%)	409/699 (58%)	36/699 (5%)
AlbXVIII	137	4-amino-4-deoxychorismate lyase (271 aa)	<i>P. aeruginosa</i>	AAG06352	81.4 bits (200)	4e-15	46/105 (43%)	65/105 (61%)	-
AlbXIX	200	McbG (187 aa)	<i>E. coli</i>	CAA30724	60.5 bits (145)	9e-09	36/141 (25%)	58/141 (40%)	37/141 (3%)
AlbXX	202	4-hydroxybenzoate synthase (202 aa)	<i>E. coli</i>	AAC77009	45.6 bits (107)	5e-04	42/161 (26%)	21/161 (13%)	-
AlbXXI	278	XabA (278aa)	<i>X. albilineans</i>	AAG28384	430 bits (1106)	0	278/278 (100%)	278/278 (100%)	-
AlbXXII	634	Heat shock protein HspG (634) Heat shock protein HspG (624)	<i>P. aeruginosa</i> <i>E. coli</i>	AAG04985 AAC73575	1051 bits (2688) 743 bits (1899)	0 0	523/634 (82%) 376/624 (60%)	588/634 (92%) 476/624 (76%)	- 4/624 (0%)

Table 5 : Comparison of conserved sequences in C domains of peptide synthetases and in putative C domains of the Alb modules

	Core	Sequences conserved in peptide synthetases*	Sequence	Alb module
5	C1	SxAQxR (L/M) (W/Y) xL	TYAQERLWLV STAQERMWFL SYAQERLWLV SLFQERLWLV SYQQERLWLV	NRPS-1 NRPS-2 NRPS-3 NRPS-4 NRPS-7
10	C2	RHExLRTxF	RHEVLRTF RHAVLRTHF RHEILRTF RHETLRTRI	NRPS-1 and NRPS-3 NRPS-2 NRPS-4 NRPS-7
15	C3	MHHxISDG (W/V) S	IHHIISDGWS IHHIVFDGWS MHHLIYDAWS MHHIICDGWS	NRPS-1 and NRPS-3 NRPS-2 NRPS-4 NRPS-7
20	C4	YxD (F/Y) AVW	YADYALW YADYARW YADYAIW YADYATW	NRPS-1 and NRPS-3 NRPS-2 NRPS-4 NRPS-7
25	C5	(I/V) Gx FVNT (Q/L) (C/A) xR	IGFFINILPLR IGLFVNTLAVR IGFFVNILAVR	NRPS-1, NRPS-3 and NRPS-4 NRPS-2 NRPS-7
30	C6	(H/N) QD (Y/V) PFE	HQSVPF HQDVPF NQALPF HRALPF	NRPS-1 and NRPS-3 NRPS-2 NRPS-4 NRPS-7
35	C7	RDxSRNPL	RDSSQIPL RDTARNPL RDTSRIP RDSSQIPL	NRPS-1 and NRPS-3 NRPS-2 NRPS-4 NRPS-7

*Sourced from Marahiel *et al.*, 1997

40 **Table 6 : Comparison of conserved sequences in A domains of peptide synthetases and in putative A domains of the Alb modules**

	Core	Sequences conserved in peptide synthetases*	Sequence	Alb module
45	A1	L (T/S) YxEL	WSYAQL LSYAQL MSYGQL FSYRQL LSYAQL	NRPS-1 and NRPS-3 NRPS-2 NRPS-5 PKS-4 NRPS-6 and NRPS-7
50	A2	LKAGxAYL (V/L) P (L/I) D	FKAGACYVPID SLCGAASVLID MKAGAAYVPID LAGGLVFAPIN LKAGGCYVPLD	NRPS-1 and NRPS-3 NRPS-2 NRPS-5 PKS-4 NRPS-6 and NRPS-7
55	A3	LAYxxYTSG (S/T) TGxPKG	LACVMVTSGSTGRPKG ?TRTIMVESGSLSSRL? PVYCIYTSGSTGSPKG PAVMICTSGSTGTPKA LAYVMYTSGSTGRPKG	NRPS-1 and NRPS-3 NRPS-2 NRPS-5 PKS-4 NRPS-6 et NRPS-7
60	A4	FDxS	FAVS FDAA FDLT FAYG FAIS	NRPS-1 and NRPS-3 NRPS-2 NRPS-5 PKS-4 NRPS-6 and NRPS-7
65				
70	A5	NxYGPTE	NNYGCTE ?AAYGNAE? NEYGPTE DGIGCTE	NRPS-1 and NRPS-3 NRPS-2 NRPS-5 PKS-4

		YIYGCTE	NRPS-6 and NRPS-7
5	A6 GELxIxGxG (V/L) ARGYL	GELHVHSGVMARGYW np GQIHIGGAGVAIGYV GSLWVRGNTLTRGYV GEVHIESLGITHGYW	NRPS-1 and NRPS-3 NRPS-2 NRPS-5 PKS-4 NRPS-6 and NRPS-7
10	A7 Y (R/K) TGD L	YKTGDM ?YKTDAL? YASGDL ?FDTRDL? YRTGDM	NRPS-1 and NRPS-3 NRPS-2 NRPS-5 PKS-4 NRPS-6 and NRPS-7
15	A8 GRxDxQVKIRGxRIELGEIE	GRQDFEVKVRGHRVDTRQVE ?GSLDVQSRIDDPRIDLCVVE? GRKDSQIKLRGYRIELGEIE ?GRMGSAIKINGCWLSPETLE? GRRDYEYKVRGYRVDVRQVE	NRPS-1 and NRPS-3 NRPS-2 NRPS-5 PKS-4 NRPS-6 and NRPS-7
20	A9 LPxYM (I/V) P	LPTYMLP ?LPDYLLP? LPEYMLP ?LGKHHYP? LPTYMLP	NRPS-1 and NRPS-3 NRPS-2 NRPS-5 PKS-4 NRPS-6 and NRPS-7
25	A10 NGK (V/L) DR	NGKLDR ?HGRVDL? NGKVNR ?SGKVIR? NGKLDT	NRPS-1 and NRPS-3 NRPS-2 NRPS-5 PKS-4 NRPS-6 and NRPS-7

30 *Sourced from Marahiel *et al.*, 1997

?: non conserved sequences

np: not present

Table 7 : Comparison of conserved sequences in PCP and TE domains of peptide synthetases and in putative PCP and TE domains of the Alb modules

	Domain	Sequences conserved in peptide synthetases*	Sequence	Alb module (domain)
5	PCP	DxFFxLGG (H/D) S (L/I)	D-FFAVGGHSLV	PKS-3 (PCP1)
			DNFFALGGHSLS	NRPS-1 and NRPS-3 (PCP2 and PCP4)
10			DNFFELGGHSLV	NRPS-2 (PCP3)
			DNFFELGGHSLS	NRPS-5 (PCP5)
15			DNFFNLGGHSLI	NRPS-6 and NRPS-7 (PCP6 and PCP7)
	TE	G (H/Y) SxG	GWSSG	NRPS-7
20	*Sourced from Marahiel <i>et al.</i> , 1997			

EXAMPLE 9: The alb carbamoyl transferase gene

albXV potentially encodes a protein of 584 aa with a predicted size of 65.2 kDa. This protein, AlbXV, is similar to BlmD, a carbamoyl transferase involved in bleomycin biosynthesis in *Streptomyces verticillus* (Du *et al.*, 2000), and to a probable carbamoyl transferase potentially expressed in *P. aeruginosa* (Table 4). High similarity of AlbXV with these proteins suggests that AlbXV is a carbamoyl transferase.

EXAMPLE 10: The alb esterase genes

albXI potentially encodes a protein of 315 aa with a predicted size of 35.9 kDa. This protein, AlbXI, exhibits low similarity to SyrC, a putative thioesterase involved in syringomycin biosynthesis by *Pseudomonas syringae* (Zhang *et al.*, 1995), and to a potential hydrolase encoded by *Streptomyces coelicolor* (Table 4). Precise function of SyrC remains unknown but SyrC is similar to a number of thioesterases, including fatty acid thioesterases,

haloperoxidases, and acyltransferases that contain a characteristic GxCxG motif. The corresponding SyrC domain GICAG is conserved in AlbXI which contains the sequence GWCQA, except that A replaces the last G, suggesting that AlbXI may be an esterase despite its low overall similarity with SyrC.

5 *albXIII* potentially encodes a protein of 317 aa with a predicted size of 34.5 kDa. This protein, AlbXIII, is similar to hypothetical proteins with unknown function from several bacteria including *Caulobacter crescentus* (Table 4). AlbXIII and these hypothetical proteins contain a GxSxG motif characteristic of serine esterases and thioesterases, the corresponding sequence in AlbXIII being GHSVG. In addition, AlbXIII presents a similarity with the 2-acetyl-1-alkylglycerophosphocholine esterase which hydrolyzes the platelet-activating factor
10 in *Canis familiaris* (Table 4), suggesting that AlbXIII is an esterase.

EXAMPLE 11: The alb methyltransferase genes

15 *albII* potentially encodes a protein of 343 aa (AlbII) with a predicted size of 37.7 kDa. *albII* is 100% identical to the *xabC* cistron, previously described as encoding an *O*-methyltransferase downstream *xabB* (Huang *et al.*, 2000a). This conclusion is based on the similarity of XabC with a family of methyltransferases that utilize S-adenosyl-L-methionine (SAM) as a co-substrate for *O*-methylation including TcmO protein from *Streptomyces glaucescens* (Huang *et al.*, 2000a). AlbII contains three highly conserved motifs of SAM-dependent methyltransferases, including the motif I involved in SAM binding (Figure 3). In the Figure, identical or similar amino acids (A=G ; D=E ; I=L=V) are shown in bold. Numbers indicate the position of the amino acid from the N-terminus of the protein. Abbreviations used in the Figure are: Sgl-TcmO and Sgl-TcmN, multifunctional cyclase-hydratase-3-*O*-Mtase and tetracenomycin polyketide synthesis 8-*O*-Mtase of *Streptomyces glaucescens*, respectively (accession number: M80674); Smy-MdmC, midecamycin-*O*-Mtase
20 of *Streptomyces mycarofaciens* (accession number: M93958); Mxa-SafC, Saframycin *O*-Mtase of *Myxococcus xanthus* (accession number: U24657); Ser-EryG, erythromycin biosynthesis *O*-Mtase of *Saccharopolyspora erythraea* (accession number: S18533); Spe-DauK, carminomycin 4-*O*-Mtase of *Streptomyces peucetius* (accession number: L13453); Sal-DmpM, *O*-demethylpuromycin-*O*-Mtase of *Streptomyces alboniger* (accession number: M74560); Shy-RapM, rapamycin *O*-Mtase of *Streptomyces hygroscopicus* (accession number: X86780); Sav-AveD, avermectin B 5-*O*-Mtase of *Streptomyces avermitilis* (accession number: G5921167), Sar-Cmet, mithramycin C-methyltransferase of *Streptomyces argillaceus* (accession number: AF077869); AlbII, putative albicidin biosynthesis C-
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Methyltransferase of *Xanthomonas albilineans* (SEQ ID No. 27) ; identical to XabC, accession number: AF239749).

Comparison of AlbII with the Genbank database revealed that AlbII, besides 100% identity to XabC, exhibited the highest degree of overall identity with MtmMII, a C-methyltransferase from *Streptomyces argillaceus* (Table 4) involved in C-methylation of the polyketide chain for mithramycin biosynthesis, suggesting that AlbII is a C-methyltransferase. XabC was not compared by Birch and co-workers with MtmMII (Huang *et al.*, 2000a) because the MtmMII sequence was not available until recently in the Genbank database. The three highly conserved motifs in SAM methyltransferases are also present in MtmMII (Figure 3), suggesting that AlbII is a C-methyltransferase SAM-dependent.

albVI potentially encodes a protein of 286 aa (AlbVI) with a predicted size of 32.1 kDa similar to several hypothetical protein from *Mycobacterium tuberculosis* (Genbank accessions n° AAK46042, AAK48238, AAK44517, AAK46218) and from *S. coelicolor* (Genbank accession n° CAC03631). AlbVI is also similar to the tetracenomycin C synthesis protein (TcmP) of *Pasteurella multocida* (Table 4). Four highly conserved motifs in TcmP and other O-methyltransferases are also present in AlbVI (Figure 4), suggesting that AlbVI is an O-methyltransferase. In the Figure, identical or similar aa (A=G ; D=E ; I=L=V ; K=R) are shown in bold. Numbers indicate the position of aa from the N-terminus of the protein. Abbreviations used in the Figure are: Sgl-tcmP, tetracenomycin C synthesis protein of *Streptomyces glaucescens* (accession number: C47127); Sme-PKS, putative polyketide synthase of *Sinorhizobium meliloti* (accession number: AAK65734); Pmu-tcmP: tetracenomycin C synthesis protein of *Pasteurella multocida* (accession number: AAK03406); Mtu-Omt: putative O-methyltransferase of *Mycobacterium tuberculosis* (accession number: AAK45444); Mlo-Hp: hypothetical protein containing similarity to O-methyltransferase of *Mesorhizobium loti* (accession number: BAB50127); Mtu-Hp1: hypothetical protein of *Mycobacterium tuberculosis* (accession number: AAK46042); Mtu-Hp2: hypothetical protein of *Mycobacterium tuberculosis* (accession number: AAK48238); Mtu-Hp3: hypothetical protein of *Mycobacterium tuberculosis* (accession number: AAK44517); AAK46218); Sco-Hp: hypothetical protein of *Streptomyces coelicolor* (accession number: CAC03631); AlbVI, putative albicidin biosynthesis O-Methyltransferase of *Xanthomonas albilineans* (this study). The three highly conserved motifs in SAM methyltransferases are not present in AlbVI, indicating that SAM is not a co-substrate of AlbVI.

EXAMPLE 12: The alb derived-benzoate products biosynthesis genes

albXVII potentially encodes a protein of 716 aa with a predicted size of 79.8 kDa. This protein, AlbXVII, is very similar to the para-aminobenzoate (PABA) synthase from *Streptomyces griseus* (Table 4). This enzyme is required for the production of the antibiotic candicidin (Criado *et al.*, 1993).

albXVIII potentially encodes a protein of 137 aa with a predicted size of 15.0 kDa. This protein, AlbXVIII, is similar to the 4-amino-4-deoxychorismate lyase (ADCL) from *P. aeruginosa* (Table 4). The function of ADCL is to convert 4-amino-4-deoxychorismate into PABA and pyruvate. The length of AlbXVIII is smaller (Table 4) than the length of ADCL and the similarity of AlbXVIII with this protein starts only at residues 161. *albXVIII* is preceded by a small ORF encoding a sequence of 59 aa similar to the first 42 amino acids of ADCL from *P. aeruginosa*. These data suggest that *albXVIII* is probably a truncated form of ADCL and probably not functional. *albXVIII* may, therefore, not be involved in albicidin biosynthesis. The region between *albXVII* and *albXVIII* was amplified by PCR from total DNA of *X. albilineans* Xa23R1 strain using primers ORFW (5'gcgagaggacaagctgctgc3') SEQ ID No. 53 and ORFY (5'cggtgaggatgcagcgctcg3') SEQ ID No. 54 and was sequenced. Resulting sequence data showed that the sequence of the PCR fragment was 100% identical to the sequence of pALB540, indicating that the recombination of *albXVIII* did not occur during cloning of the genomic fragment in pALB540.

albXX potentially encodes a protein of 202 aa with a predicted size of 22.6 kDa. This protein AlbXX is similar to the 4-hydroxybenzoate synthase potentially involved in ubiquinone biosynthesis by *Escherichia coli* (Siebert *et al.*, 1992).

EXAMPLE 13: The alb regulatory genes

albIII potentially encodes a protein of 167 amino acids with a predicted size of 17.8 kDa that is similar to the transcription factors ComA of different bacteria such as *E. coli* and *B. licheniformis* (Table 4). ComA transcription factors appear to be involved in regulation of antibiotic production in bacteria. In *E. coli*, a gene similar to *comA* is present in the enterobactin biosynthesis gene cluster (Liu *et al.*, 1989). In *B. subtilis*, ComAB was described as a probable positive activator of lichenysin synthetase transcription (Yakimov *et al.*, 1998) and a gene similar to *comA* was shown to be essential for bacilysin biosynthesis (Yazgan *et al.*, 2001). These data suggest that AlbIII regulates transcription of genes involved in albicidin biosynthesis.

albVIII potentially encodes a protein of 330 aa with a predicted size of 37.7 kDa. This

protein, AlbVIII, is very similar to the SyrP like protein from *S. verticillus* and to SyrP protein from *P. syringae* (Table 4). SyrP participates in a phosphorylation cascade controlling syringomycin synthesis (Zhang *et al.*, 1997) and the *syrP* like gene was described in the *S. verticillus* bleomycin biosynthetic gene cluster (Du *et al.*, 2000). These data suggest that AlbVIII regulates albicidin biosynthesis in *X. albilineans*.

EXAMPLE 14: The alb resistance genes

albXIV potentially encodes a protein of 496 aa with a predicted size of 52.7 kDa. This protein, AlbXIV, is 100% identical to AlbF isolated from *X. albilineans* strain Xa13 (GenBank Accession AF403709; direct submission by Bostock and Birch and described as "a putative albicidin efflux pump which confers resistance to albicidin in *E. coli*"). AlbXIV and AlbF are closely related to a family of transmembrane transporters involved in antibiotic export and antibiotic resistance in many antibiotic-producing organisms. AlbXIV and AlbF exhibited the highest degree of overall identity with the putative transmembrane efflux protein from *S. coelicolor* (Table 4). These data suggest that AlbXIV and AlbF may be involved in albicidin resistance by transporting the toxin out of the bacterial cells that produce it. Alternatively, AlbXIV and AlbF may simply play a role in antibiotic secretion and/or plant pathogenesis to effect the transport of albicidin outside of producing cells.

albXIX potentially encodes a protein of 200 aa with a predicted size of 22.8 kDa. This protein, AlbXIX, is similar to the McbG protein from *E. coli* (Table 4). In *Enterobacteriae*, the McbG protein, together with two other proteins (McbE and McbF), was shown to cause immunity to the peptide antibiotic microcin B17 which inhibits DNA replication by induction of the SOS repair system (Garrido *et al.*, 1988). McbE and McbF proteins serve as a pump for the export of the active antibiotic from the cytoplasm, whereas a McbG alone also provides some protection: a well-characterized deficient-immunity phenotype is exhibited by microcin B17-producing cells in the absence of the immunity gene *mcbG* (Garrido *et al.*, 1988). The significant similarity between AlbXIX and McbG, together with the fact that albicidin also blocks DNA replication (Birch and Patil, 1985a) suggests that AlbXIX confers immunity against albicidin in *X. albilineans*.

EXAMPLE 15: Transposition proteins

albV is 100% identical to the *thp* gene described in a divergent position upstream from *xabB* (Huang *et al.*, 2000a). The *thp* gene potentially encodes a protein of 239 aa displaying significant similarity to the IS21-like transposition helper proteins. In *X. albilineans* strain

LS155 from Australia, insertional mutagenesis of *thp* blocked albicidin production, but *trans*-complementation failed, indicating the involvement in albicidin production of a downstream gene in the *thp* operon (Huang *et al.*, 2000a).

albXVI potentially encodes a protein of 88 aa with a predicted size of 9.8 kDa similar to the transposases from several bacteria such as *Xanthomonas axonopodis* or *Desulfovibrio vulgaris* (Table 4).

The presence of transposition proteins in the XALB1 cluster is probably a remnant from a past transposition event that may have contributed to the development of the albicidin XALB1 cluster.

EXAMPLE 16: Unknown functions

AlbX potentially encodes a protein of 83 aa with a predicted size of 9.4 kDa. This protein, AlbX, is similar to an hypothetical protein from *P. aeruginosa* and to the MbtH protein from *Mycobacterium tuberculosis*. MbtH is a protein with unknown function found in the mycobactin gene cluster (Quadri *et al.*, 1998). A MbtH-like protein with unknown function was also described in the bleomycin biosynthetic gene cluster of *S. verticillus* (Du *et al.*, 2000). These data suggest that AlbX is involved in albicidin biosynthesis but its function remains unknown.

albXII potentially encodes a protein of 451 aa with a predicted size of 51.6 kDa. This protein, AlbXII, is very similar to a protein of 55 kDa encoded by the *boxB* gene in *Azoarcus evansii* (Table 4). This protein is a component of a multicomponent enzyme system involved in the hydroxylation of benzoyl CoA, a step of aerobic benzoate metabolism in *Azoarcus evansii*, but its function remains unknown (Mohamed *et al.*, 2001).

EXAMPLE 17: Prediction of amino acid specificity of Alb NRPS modules

In NRPSs, specificity is mainly controlled by A domains which select and load a particular amino-, hydroxy- or carboxy-acid unit (Marahiel *et al.*, 1997). The substrate-binding pocket of the phenylalanine adenylation (A) domain of the gramicidin S synthetase (GrsA) from *Brevibacillus brevis* was recently identified by crystal structure analysis as a stretch of about 100 amino acid residues between highly conserved motifs A4 and A5 (Conti *et al.*, 1997). Based on sequence analysis of known A domains, in relation to the crystal structure of the GrsA (Phe)substrate binding pocket, similar models have been published to predict the amino acid substrate which is recognized by an unknown NRPS A domain (Challis *et al.*, 2000; Stachelhaus *et al.*, 1999). These models postulate specificity-conferring codes for

A domains of NRPS consisting of critical amino acid residues putatively involved in substrate specificity. The model proposed by Marahiel and co-workers (Stachelhaus *et al.*, 1999) defined a signature sequence consisting of ten amino acids lining with the ten residues of the phenylalanine-specific binding pocket located at positions 235, 236, 239, 278, 299, 301, 322, 330, 331 and 517 in the GsrA (Phe) sequence (accession number: P14687). The model proposed by Townsend and co-workers (Challis *et al.*, 2000) uses only the first eight of these critical residues.

Preliminary specificity assignments of albicidin synthase AlbI, AlbIV, AlbVII and AlbIX NRPS modules were made by comparison of complete sequences between conserved motifs A4 and A5 with sequences in the Genbank database. The corresponding sequence of the AlbIV NRPS-5 module is most related to domain 5 of bacitracin synthase 3 (BA3) from *B. licheniformis* that was suggested to activate Asn (Konz *et al.*, 1997). Corresponding sequences of AlbI and AlbIX NRPS-1, NRPS-3, NRPS-6 and NRPS-7 modules, apart from their very high similarity with XabB, exhibited the highest degree of overall identity (39%) with the Blm NRPS2 module of the biosynthetic gene cluster for bleomycin from *S. verticillus* that specifies for β -Alanine (Du *et al.*, 2000). The corresponding sequence of AlbVII PKS-4 produced the highest significant alignment with acetate-CoA ligase from *Sulfolobus solfataricus* (Genbank accession number: AAK41550), aryl-CoA ligase from *Comamonas testosteroni* (Genbank accession number: AAC38458) and 4-hydroxybenzoate-CoA ligase from *R. palustris*. The sequence between motifs A4 and A5 of the AlbI NRPS-2 could not be significantly aligned with any sequence present in the Genbank database. Comparison of this sequence with the corresponding sequence of GsrA (Phe) revealed that parts of the putative core and structural "anchor" sequences of AlbI NRPS-2 are deleted (Figure 5), suggesting that the AlbI NRPS-2 substrate binding pocket is not functional. In the Figure, amino acids of the six Alb NRPSs and of Alb PKS-4 that are identical or similar to GsrA or Blm sequences (A=G; D=E; I=L=V; R=K) are shown in bold. Amino acids underlined in the GsrA sequence correspond to the phenylalanine-specific binding pocket. The positions of these amino acids in the GsrA primary sequence are indicated at the top of the figure. Amino acids underlined in the other sequences correspond to putative constituents of binding pockets, aligned with the seven residues of the phenylalanine-specific binding pocket of GsrA. Shaded amino-acids correspond to the putative core sequences and structural 'anchors' based on comparison with the GsrA binding-pocket structure.

Alignment of the primary sequence between conserved motifs A4 and A5 of the AlbI, AlbIV, AlbVII and AlbIX NRPS-1, NRPS-3, NRPS-5, NRPS-6, NRPS-7 and PKS-4 modules

with the corresponding sequence of GrsA (Phe) (Figure 5) revealed the putative constituents of binding pockets that constitute the codes as defined by Marahiel and co-workers (Stachelhaus *et al.*, 1999). These codes were compared with those of proteins most related to the sequence between the A4 and A5 motifs (Table 8) and were analyzed with the model proposed by Townsend and co-workers (Challis *et al.*, 2000, <http://jhunix.hcf.jhu.edu/~ravel/nrps/>). Using these codes, we were able to predict the Asparagine specificity of the AlbIV NRPS-5 module. The AlbIV NRPS-5 signature is 100% identical to BacC-M5 (Asn) and TyrC-M1 (Asn) codes identified in bacitracin synthetase 3 from *B. licheniformis* and in tyrocidine synthetase 3 from *B. brevis* (Table 8). The AlbIV NRPS-5 signature is also identical to the Asn code defined by Marahiel and co-workers (1997), except that I is replaced by L at position 299 (Table 8). The Albl and AlbIX NRPS-1, 3, 6 and 7 signatures did not match any of those defined by Marahiel and co-workers (1997). Similarly, convincing predictions using the model proposed by Townsend and co-workers were not obtained either (Challis *et al.*, 2000, <http://jhunix.hcf.jhu.edu/~ravel/nrps/>). The Albl and AlbIX NRPS-1, 3, 6 and 7 signatures diverged from all NRPS signatures previously described, except from the XabB signature that is identical to the Albl NRPS-1 and 3 signatures. The signature most closely related to Albl NRPS-1 and 3 specify Pro and the signature most closely related to AlbIX NRPS-6 and 7 specify Ser, but the degree of similarity in both cases is very weak (Table 8). The PKS-4 signature is similar to the Albl NRPS-1 and NRPS-3 signatures at positions 235, 299 and 301.

Analysis of alignment of the primary sequence between conserved motifs A4 and A5 of the Albl and AlbIX NRPS-1, NRPS-3, NRPS-6 and NRPS-7 modules with the corresponding sequences of the bleomycin synthase (Blm) NRPS2 (β -Ala) and gramicidin S synthetase (GrsA) modules (Figure 5) revealed that (i) sequences of Albl NRPS-1 and Albl NRPS-3 differ only at the level of two residues that are not involved in substrate binding, (ii) sequences of AlbIX NRPS-6 and AlbIX NRPS-7 are 100% identical, (iii) sequences of Albl NRPS-1 and Albl NRPS-3 are very similar to sequences of AlbIX NRPS-6 and AlbIX NRPS-7 but differ at the level of five putative constituents of binding pocket, (iv) Albl and AlbIX NRPS residues, which are similar to residues of Blm NRPS2 (β -Ala) or GrsA (Phe), are essentially located at the level of the putative core sequences and structural "anchor", and differ at the level of putative constituents of the binding pocket.

Binding-pocket constituents forming the NRPS signatures have been classified into three subgroups according to their variability among 160 specificity-conferring signature sequences (Stachelhaus *et al.*, 1999): (i) invariant residues Asp235 and Lys517 that mediate

key interactions with the α -amino and α -carboxylate group of the substrate, respectively; (ii) moderately variant residues in positions 236, 301 and 330 which correspond to aliphatic amino acids and which may modulate the catalytic activity and fine-tune the specificity of the corresponding domains; (iii) highly variant residues in positions 239, 278, 299, 322 and 331 which may facilitate substrate specificity. AlbI and AlbIX NRPS-1, 3, 6 and 7 signatures are not totally in accordance with this classification. Invariant residue Lys517 is conserved in the four NRPS signatures, indicating the presence of an α -carboxylate group in the corresponding substrates. The Asp235Ala alteration is not consistent with an α -amino acid substrate. Birch and co-workers (Huang *et al.*, 2001) assumed that the initial alanine residue in the XabB signature was consistent with a nonproteinogenic hydroxy acid substrate by analogy with the initial glycine in the signature of the hydroxyisovaleric-acid (HVCL) loading domain of enniatin synthetase. The presence of an initial Alanine in the AlbVII PKS-4 signature (Figure 8) and in several 4-hydroxybenzoate-CoA ligase codes may confirm this hypothesis. However, the HVCL loading domain of enniatin synthetase (Table 8) and AlbVII PKS-4 are not preceded by a C domain and are not followed by a PCP domain, in contrast to the AlbI and AlbIX NRPS-1, 3, 6 and 7 modules. An Asp235Val alteration was recently described in the β -Ala specificity-conferring code (Du *et al.*, 2000, Table 8), suggesting that the substrate of AlbI and AlbIX NRPS-1, 3, 6 and 7 modules may be different from α -amino acids but may contain an amino group. Residue 236 is an aliphatic residue (Val or Ile) in all AlbI and AlbIX NRPS-1, 3, 6 and 7 signatures. Residue 301 is an aliphatic residue (Ala) in the AlbI NRPS-1 and 3 codes, but it is a Ser in the AlbIX NRPS-6 and 7 signatures. Residue 330 is not an aliphatic residue in the four NRPS signatures but an Asp. Similar alterations are present in the β -Ala code: residue 236 is an Asp, residue 301 is a Ser and residue 330 is an aliphatic amino acid. Concerning highly variable residues, AlbI NRPS-1 and 3 signatures differ from AlbIX NRPS-6 and 7 signatures at residue positions 299, 322 and 331, confirming that both types of NRPS modules specify different substrates.

Table 8 : Comparison of signature sequences, as defined by Marahiel and co-workers (Stachelhaus *et al.*, 1999), derived from sequences between the A4 and A5 domains of the AlbI, AlbIV, and AlbIX NRPS modules with those of Tyr-M1 (Pro) (Tyrocidine synthetase 2 module 1, accession number: AAC45929), VirS (Pro) (Virginiamycin S synthetase, accession number : CAA72310), HVCL (hydroxyisovaleric acid-CoA ligase, ACL1 enniatin synthetase, accession number: S39842), EntF-M1 (Ser) (Enterobactin synthase, accession number: AAA92015), β -Ala code (β -Ala selectivity-conferring code defined by Du *et al.*, 2000),

BacC-M5 (Asn) (Bacitracin synthetase 3, accession number: AAC06348), TyrC-M1 (Asn) (Tyrocidine synthetase 3, accession number: AAC45930) and Asn code (Asn selectivity-conferring code defined by Marahiel and co-workers (Stachelhaus *et al.*, 1999). Amino acids of AlbI NRPS-1 and NRPS-3 signatures identical or similar to TyrB-M1 (Pro), VirS (Pro) and HVCL signatures (A=G; D=E; I=L=V; R=K) are shown in bold. Amino acids of AlbIX NRPS-6 and NRPS-7 signatures identical or similar to Vir (Pro) and Blm (β -Ala) signatures (A=G; D=E; I=L=V; R=K) are shown in bold. Variability: 0 indicates invariant residues, +/- moderately variant residues and ++ highly variant residues.

		Position in GsrA (Phe) and variability									
Domains		235	236	239	278	299	301	322	330	331	517
		0	+/-	++	++	++	+/-	++	+/-	++	0
15	Alb NRPS-1	A	V	K	Y	V	A	N	D	A	K
	Alb NRPS-3	A	V	K	Y	V	A	N	D	A	K
	TyrB-M1 (Pro)	D	V	Q	S	I	A	N	V	V	K
	VirS (Pro)	D	V	Q	Y	A	A	H	V	M	K
	HVCL	G	A	L	H	V	V	G	S	I	K
20	Alb NRPS-6	A	I	K	Y	F	S	I	D	M	K
	Alb NRPS-7	A	I	K	Y	F	S	I	D	M	K
	VirS (Pro)	D	V	Q	Y	A	A	H	V	M	K
	EntF-M1 (Ser)	D	V	W	H	F	S	L	V	D	K
	β -Ala code	V	D	W	V	I	S	L	A	D	K
25	Alb NRPS-5	D	L	T	K	I	G	E	V	G	K
	BacC-M5 (Asn)	D	L	T	K	I	G	E	V	G	K
	TyrC-M1 (Asn)	D	L	T	K	I	G	E	V	G	K
	Asn code	D	L	T	K	L	G	E	V	G	K

EXAMPLE 18: Identification of putative promoters and putative terminators in XALB1

Putative rho independent terminators were identified downstream from *albIV* and *albXVI* using the Terminator program (Brendel and Trifonov, 1984), run with the Wisconsin Package™ GCG software (Figure 6). In the Figure, dashes indicate palindromic sequences. Symbols used in the Figure are: P, Primary structure value of putative terminator (minimum threshold value of 3.5 represents 95 percent of known, factor-independent, prokaryotic terminators); S, Secondary structure value of putative terminator. The presence of these

terminators confirmed the proposed genetic organization of operons 1 and 3. A rho-independent terminator was identified in the intergenic region between *albXVII* and *albXVIII*, suggesting that the group of genes initially supposed to be organized in operon 4 may be in fact organized in two operons, operon 4 formed by *albXVII* and operon 5 by *albXVIII* – *albXX*. No putative rho independent terminator was found downstream from *albIX* and from *albXX*.

The 236 bp region between *albI* (operon 1) and *albV* (operon 2) is 100% identical to the sequence between *xabB* and *thp* genes that is assumed to contain a bidirectional promoter (Huang *et al.*, 2000a and 2001), suggesting that transcription of operon 1 and 2 is regulated by the same bidirectional promoter region (Huang *et al.*, 2001).

The 412 bp region comprised between *albX* (operon 3) and *albXVII* (operon 4) also contains a putative bidirectional promoter (Figure 7). In the Figure, the sequence of putative promoters are underlined, and putative ATG or TTG start codons are in bold. The closest matches (TTGACA-18x-TATAGT) to the consensus -35 (TTGACA) and -10 (TATAAT) sequences for *E. coli* σ^{70} promoters occurs 61 bp upstream from *albX* (operon 3). The closest matches (TTCAGA-19x-TATACA) to the consensus sequences for *E. coli* σ^{70} promoters occur 320 bp upstream from *albXVII* (operon 4). The region between *albXVII* and *albXVIII* lacks any apparent *E. coli* σ^{70} promoter. However, the sequence immediately upstream from *albXIX*, corresponding to the coding sequence of *albXVIII*, potentially contains an unidirectional promoter (Figure 7). The closest match (TTGCTC-19x-TATATT) to the consensus sequences for *E. coli* σ^{70} promoters occurs 33bp upstream from *albXIX*. The presence of a terminator downstream from *albXVII* and of a promoter upstream from *albXIX* suggests that *albXVIII* is not transcribed and that *albXIX* and *albXX* form operon 5.

EXAMPLE 19: Cloning of the XALB2 gene cluster

The 6 kb *EcoR* I fragment carrying Tn5 and flanking sequence from strain AM37 was cloned in pBR325 and the obtained plasmid was designated pAM37 (Table 1). A 1.1 kb *Hind* III-*Hind* III DNA fragment from pAM37, named PR37 (Table 1), was labeled with 32 P and used to probe the 845 clones from the genomic library of *X. albilineans* strain Xa23R1, previously described (Rott *et al.*, 1996). Eight new cosmids hybridized to this probe and restored albicidin production in mutant AM37. One of these cosmid, pALB389, carrying an insert of about 37 kb (Table 1), was used for complementation studies of the five mutants not complemented by pALB540 and pALB571. Cosmid pALB389 complemented mutants AM10

and AM37. Mutant AM10 was initially thought to be complemented by pALB639 (Rott et al., 1996). However, further complementation studies showed that mutant AM10 was not complemented by pALB639, and that only three mutants (AM12, AM13 and AM36) were complemented by pALB639 containing the third genomic region XALB3 involved in albicidin production. A 3 kb *EcoRI*-*EcoRI* DNA fragment from pALB389 that hybridized with probe PR37 was sub-cloned in pUFR043 (Table 1). The resulting plasmid pAC389.1 complemented mutants AM10 and AM37, confirming that the second region involved in albicidin production, XALB2, was present in the 3 kb insert of pAC389.1.

EXAMPLE 20: Cloning of the XALB3 gene cluster

Cosmid pALB639, carrying an insert of 36 kb (Rott et al., 1996; Table 1) was used as a probe to compare the *EcoRI* restriction profiles of *X. albilineans* strain Xa23R1 with those of mutants AM12, AM13 and AM36 which were supposed to be mutated in the XALB3 gene cluster. An 11 kb band which was found in strain Xa23R1 but not in the three mutants was supposed to contain the XALB3 gene cluster. A 9.7 kb *EcoRI* DNA fragment purified from cosmid pALB639 also used as a probe in Southern blot analyse revealed the same 11 kb band. This 9.7 kb *EcoRI* DNA fragment was sub-cloned in pUFR043 (Table 1) and the resulting plasmid pAlb639A complemented mutants AM12, AM13 and AM36. The third region involved in albicidin production, XALB3, was therefore present in the 9.7 kb insert of pAlb639A.

EXAMPLE 21: Sequencing of the Tn5 insertional site of *tox*⁻ mutants located in XALB2 and XALB3 and sequencing of the genomic regions XALB2 and XALB3

In Figure 8, E, H, Sa and S indicate restriction endonuclease cut sites for *EcoRI*, *HindIII*, *Sall* and *Sau3AI*, respectively. The DNA inserts carried by plasmids pAC389.1, pALB639A or pEV639 are represented by the bars at the top of the respective figures. Positions of the Tn5 insertional sites of mutants AM10, AM12, AM36 and AM37 were determined by sequencing and are indicated by vertical arrows. The DNA region corresponding to the Tn5 flanking regions in pAM10, pAM12.1, pAM36.2 and pAM37 and in the PR37 DNA fragment are represented by the bars at the bottom of the respective figures. The location and direction of *albXXI* and *albXXII* are indicated by thick black arrows. The location of other orfs in XALB2 similar to those described by Huang et al. (2000b) are indicated by thick white arrows.

The 7 kb *EcoR* I fragment carrying Tn5 and flanking sequence from strain AM10 was cloned in pBluescript II KS (+), and the obtained plasmid was designated pAM10 (Table 1). The sequences between *EcoR*I sites and the Tn5 insertional site of mutants AM10 and AM37 were sequenced from the resulting plasmids pAM10 and pAM37, respectively. The complete double-strand nucleotide sequence of the 2,986 bp *EcoR* I – *EcoR* I insert of pAC389.1 was determined from sequencing results of plasmids pAC389.1, pAM10 and pAM37 (Figure 8). The Tn5 insertional sites of mutants AM10 and AM37 were sequenced from plasmids pAM10 and pAM37 (Table 1), respectively, using the sequencing primer GUSN (5'tgccacaggccgctcgagt3') that annealed 135 bp downstream from the insertional sequence IS50L of Tn5-*gusA*. The Tn5 insertional site of AM10 and AM37 was located at position 2107 and 1882, respectively.

The *EcoR*I fragments carrying Tn5 and the flanking sequences from mutants AM12 and AM36 were cloned in pBR325 (Rott *et al.*, 1996; Table1). The sequences between *EcoR*I site and the Tn5 insertional site of mutants AM12 and AM36 were sequenced from the resulting plasmids pAM12.1 and pAM36.2, respectively. The complete double-strand nucleotide sequence of the 9,673 bp *EcoR* I – *Sau*3A I insert of pALB639A was determined from the sequencing results of plasmids pAM12.1, pAM36.2 and pALB639A (Figure 8). The Tn5 insertional site of mutants AM12 and AM36 was sequenced from plasmids pAM12.1, pAM36.2 using the sequencing primer GUSN (5'tgccacaggccgctcgagt3') that annealed 135 bp downstream from the insertional sequence IS50L of Tn5-*gusA*. The Tn5 insertional site of AM12 and AM36 was located at position 6500 and 7232, respectively (Figure 8).

EXAMPLE 22: Homology analysis and genetic organization of XALB2 (Figure 8).

The sequence of 2986 bp containing XALB2 is 99.4% identical to the sequence of 2989 bp containing *xabA* described in *X. albilineans* strain LS155 from Australia (Huang et al., 2000b; accession number AF191324). The Tn5 insertional site of mutant LS156 described in *xabA* is 15 bp upstream from the insertional site of AM37. The orf disrupted in AM37 and AM10, designed albXXI, is identical to *xabA* except a C which replaces a T at position 1642. albXXI potentially encodes a protein of 278 aa with a predicted size of 29.3 kDa which is 100% identical to the potential product of *xabA*, described as a phosphopantetheinyl transferase (Huang et al., 2000b). Region XALB2 contains three additional orfs (orf1, orf2, and orf3) similar to those described by Huang et al., (2000b; orf, *rsp6* and *aspT*). orf2 and orf3 are 100% identical to *rsp6* and *aspT* respectively, and orf1 is similar to but smaller than orf. There are no close matches to the *E. coli* γ 70 promoter –10 (TATAAT) and –35 (TTGACA)

consensus sequence, and no putative RBS site upstream from the putative start codon ATG of *albXXI*. The putative factor-independent transcription site described at 42 bp downstream from the TGA stop codon of *xabA* (Huang et al., 2000b) is also present at the same position downstream from *albXXI*.

EXAMPLE 23: Homology analysis and genetic organization of XALB3 (Figure 8).

The orf disrupted in mutants AM12 and AM36 was located between nucleotide 6090 (ATG) and 8009 (TAA) and was designed *albXXII*. The first ATG at position 6090 is not preceded by a putative ribosome binding sequence, suggesting that the start codon is the ATG at position 6105 which is preceded at position -9 by the putative ribosome binding site sequence GGAG. A putative rho independent terminator was identified at position 8082, 73 b downstream from *albXXII* (figure 6). There are no close matches to *E. coli* σ^{70} promoter -10 (TATAAT) and -35 (TTGACA) consensus sequence upstream from the putative start codon. The *SalI* DNA fragment corresponding to DNA sequence from nucleotide 5510 to nucleotide 8124, which contains the 595 bp upstream from the putative start codon, the orf *albXXII* and the putative rho independent terminator, was sub-cloned in pUFR043 in the opposite direction to LacZ (Table 1). The resulting plasmid pEV639 (table 1) complemented mutants AM12, AM13 and AM36, confirming that (i) the third region involved in albicidin production, XALB3, was present in the insert of pEV639; (ii) *albXXII* is not transcribed as part of a larger operon ; and (iii) the 595 bp upstream the putative start codon contain a promoter.

The potential product of *albXXII*, designated AlbXXII, is a protein of 634 aa with a predicted size of 71.5 kDa. This protein is very similar to the heat shock protein HtpG from *Pseudomonas aeruginosa* (identities = 82%) and from *Escherichia coli* (identities = 60%)(table 4). The methionine encoded by the putative start codon at position 6105 was aligned with the first aminoacid of the heat shock protein HtpG from *Pseudomonas aeruginosa*, confirming that *albXXII* initiates at position 6105.

The invention includes the isolation and sequencing of a region of 55,839 bp from *X. albilineans* strain Xa23R1 containing the major gene cluster XALB1 involved in albicidin production. Analysis of this region allowed us to predict the genetic organization of the gene cluster XALB1 which contains 20 ORFs grouped in four or five operons (Figure 1). Because *albXVIII* is a truncated gene, XALB1 genes may be organized in five operons. Therefore, we will from now on consider *albXVII* as part of operon 4 and *albXIX* and *albXX* as part of operon 5. Similar operon-type organizations for antibiotic biosynthesis clusters are well

known and have been postulated to facilitate cotranslation of genes within the operon to yield equimolar amounts of proteins for optimal interactions to form the biosynthesis complexes (Cane, 1997). Overlapping genes involved in the same process are also quite common in bacteria (Normark *et al.*, 1983).

5 Previous results of transposon mutagenesis and complementation studies (Rott *et al.*, 1996; Rott, unpublished results) are in accordance with the predicted genetic organization of XALB1 described in this study, and allowed us to establish that operons 1, 2 and 3 are involved in albicidin biosynthesis: (i) Tox⁻ mutants with a Tn5-*gusA* insertion site located in DNA fragments B, C, G and D were complemented by cosmid pALB571 and not by cosmid
10 pALB540, confirming that cosmid pALB571 potentially contains the entire operon 1; (ii) Tox⁻ mutants with a Tn5-*gusA* insertion site located in DNA fragments A and H were complemented by both cosmids pALB540 and pALB571, confirming that both cosmids potentially contain the entire operon 2; (iii) mutant XaAM1 with a Tn5-*gusA* insertion site located in DNA fragment J is the only Tn5 Tox⁻ mutant complemented by cosmid pALB540
15 and not by cosmid pALB571, confirming that cosmid pALB540 potentially contains the entire operon 3. Our mutagenesis studies did not confirm that operons 4 and 5 are required for biosynthesis of albicidin. The para-aminobenzoate (PABA) is required for the growth of many bacteria probably including *X. albilineans*, suggesting that a mutation in *albXVII* may be lethal and explaining why we did not obtain any mutant disrupted in this gene.

20 Putative bidirectional promoters were identified between operons 1 and 2 (Huang *et al.*, 2001) and between 3 and 4 (Figure 7), confirming the prediction of genetic organization of XALB1. The region upstream from operon 1 is 100 % identical to the region upstream from the *xabB* start codon which was described as a functional promoter during the phase of albicidin accumulation in Australian strain Xa13 of *X. albilineans* (Huang *et al.*, 2001).
25 Involvement of several operons in albicidin biosynthesis suppose that they are transcribed during the same time. Promoter activities of regions upstream from putative operons 2, 3, 4 and 5 need to be determined to precise if these promoters are functional during the same growth phase of *X. albilineans* as the promoter upstream from operon 1.

30 Potential rho-independent transcription terminators were identified downstream from operons 1, 3 and 4 (Figure 6) confirming prediction of the genetic organization of these three operons. Because operons 2 and 5 are convergent (Figure 1) and separated by a very short region of 22 bp between *albIX* and *albXX*, stop codons may allow transcription termination in the absence of sequences corresponding to potential rho-independent transcription terminators downstream from these operons. It is quite possible that simultaneous transcription of

operons 2 and 5 involving the presence of two RNA polymerases (one on each strand of DNA) may cause RNA polymerases to pause at the end of each operon because of steric interference between both polymerase complexes in the same short region.

5 The presence of putative RBSs upstream of the ATG start codons of all ORFs, except for *albXVIII*, suggests that these ORFs are translated in *X. albilineans*. The absence of a canonical RBS upstream from *albXVIII* further indicates that this ORF is probably not expressed. GTG and TTG codons (usually valine and leucine codons) generally serve as procaryotic start codons when located near the 5' end of an RNA message, but GTG start codons were also described far from the 5' end of messenger RNA in the bacitracin biosynthesis cluster of *B. licheniformis* (Genbank accession n° AF184956) or in the bleomycin biosynthetic gene cluster of *S. verticillus* (Genbank accession n° AF210249). This is in accordance with the fact that the two potential TTG start codons are the first start codons in operons 1 and 4 of XALB1, and that the two potential GTG start codons initiate internal cistrons. The *albl* and *albXVII* genes, like *xabB* (Huang *et al.*, 2001), use TTG as a start codon, which may impose post-transcriptional control of the rate of gene product formation (McCarthy and Gualerzi, 1990).

20 The predicted genetic organization of operons 1 and 2 presents similarities with the organization of the region involved in albicidin production in strain Xa13 of *X. albilineans* from Australia (Huang *et al.* 2000a, Huang *et al.*, 2001). This latter region also contains two divergent operons involved in albicidin production, one comprising the *xabB* gene (similar to *albl*, but with a large deletion) and the *xabC* gene (100% identical to *albII*) and the other containing *thp* gene (100% identical to *albV*). In addition, the sequence between the two operons in strain Xa13 is 100% identical to the sequence between operons 1 and 2, indicating that both clusters are controlled by the same bidirectional promoter. However, transposon mutagenesis studies of Xa13 showed no evidence of another cistron downstream of *xabC* that may be involved in albicidin production (Huang *et al.*, 2000a), suggesting that the Xa13 *xab* operon differs from the Xa23R1 operon 1, which contains two additional genes downstream from *albII* that are potentially involved in albicidin production (*albIII* and *albIV*; refer Figure 1).

30 Homology analysis revealed that four NRPS and/or PKS genes are present in XALB1 (Figure 2), and these genes may be involved in the biosynthesis of the albicidin polyketide-polypeptide backbone (*albl*, *albIV*, *albVII* and *albIX*). NRPS and PKS enzymes are generally organized into repeated functional units known as modules, each of which is responsible for a discrete stage of polyketide or polypeptide chain elongation (Cane and Walsh, 1999). Each

PKS or NRPS module is made up of a set of three core domains, two of which are catalytic and one of which acts as a carrier, and together are responsible for the central chain-building reactions of polyketide or polypeptide biosynthesis. Both PKS and NRPS core domains utilize analogous acyl-chain elongation strategies in which the growing chain, tethered as an acyl-S-enzyme to the flexible 20 Å long phosphopantetheinyl arm of an acyl carrier protein (ACP) or peptidyl carrier protein (PCP) domain, acts as the electrophilic partner that undergoes attack by a nucleophilic chain-elongation unit, a malonyl- or aminoacyl-S-enzyme derivative, respectively, itself covalently bound to a downstream ACP/PCP domain. In the case of a PKS, the fundamental chain-elongation reaction, a C-C bond-forming step, is mediated by a ketosynthase (KS) domain that catalyzes the transfer of the polyketide acyl chain to an active-site cysteine of the KS domain, followed by condensation with the methylmalonyl- or malonyl-S-ACP by a decarboxylative acylation of the malonyl donor unit. An additional essential component of the core PKS chain-elongation apparatus is an associated acetyltransferase (AT) domain, which catalyzes the priming of the donor ACP sidearm with the appropriate monomer substrate, usually methylmalonyl- or malonyl-CoA. The comparable core domains of an NRPS biosynthetic module function in a chemically distinct but architecturally and mechanistically analogous fashion. In the latter case, the key chain-building reaction, a C-N bond-forming reaction, involves the generation of the characteristic peptide bond by nucleophilic attack of the amino group of an amino acyl-S-PCP donor on the acyl group of an upstream electrophilic acyl- or peptidyl acyl-S-PCP chain, catalyzed by a condensation (C) domain. In functional analogy to the PKS AT domain, the core of the NRPS module utilizes an adenylation (A) domain to activate the donor amino-acid monomer as an acyl-AMP intermediate, which is then loaded onto the downstream PCP side chain. Both the AT and A domains of the respective PKS and NRPS modules act as important gatekeepers for polyketide or polypeptide biosynthesis, exhibiting strict or at least high specificity for their cognate malonyl-CoA, methylmalonyl-CoA or amino acid substrates. In addition to the basic subset of core domains, each PKS or NRPS also has a special set of dedicated domains responsible both for the initiation of acyl-chain assembly by loading of a starter unit onto the first, furthest upstream PKS/NRPS module, as well as a chain-terminating thioesterase (TE) domain, most often found fused to the last module, that is responsible for detachment of the most downstream covalent acyl enzyme intermediate and off-loading of the mature polyketide or polypeptide chain (Cane and Walsh, 1999).

XALB1 potentially encodes four PKS modules and seven NRPS modules. Most of the bacterial NRPS gene clusters described up to now are organized in operon-type structures,

encoding multi modular NRPS proteins with individual modules organized along the chromosome in a linear order that parallels the order of amino acids in the resultant peptide, following the "colinearity rule" for the NRPS-template assembly of peptides from amino acids (Cane, 1997; Cane *et al.*, 1998; Cane and Walsh, 1999; von Döhren *et al.*, 1999). PKS and NRPS modules are apparently not organized according to this "colinearity rule" for albicidin biosynthesis because of the following features : (I) NRPS and PKS genes are expressed in two divergent operons; (ii) no AT domain was identified in PKS-2 and PKS-3 domains, suggesting involvement of a separate enzyme ; (iii) the A domain of NRPS-2 is not functional, suggesting the involvement of a *trans*-acting A domain ; (iv) a single chain-terminating TE domain was identified in XALB1 which may be responsible of the release of the full length albicidin polyketide-polypeptide backbone from the enzyme complexes. Exception to the "colinearity rule" has also been shown for the syringomycin synthetase of *P. syringae* (Guenzi *et al.*, 1998), for the exochelin synthetase of *Mycobacterium smegmatis* (Yu *et al.*, 1998) and for the bleomycin synthetases of *S. verticillus* (Du *et al.*, 2000).

On the basis of the deduced functions of individual NRPS and PKS domains we have aligned the four PKS and the seven NRPS modules to suggest two different putative linear models for the synthesis of the albicidin polyketide-peptide backbone (Figure 9). In the Figure, NRPS and PKS domains are abbreviated as follows: A, adenylation; ACP, acyl carrier protein; AL, acyl-CoA ligase; AT, acyltransferase; C, condensation; HBCL, hydroxybenzoate-CoA ligase; KR, ketoreductase; KS, ketoacyl synthase; PCP, peptidyl carrier protein. Asn designates asparagine. X1 and X2 indicate substrates incorporated by NRPS -1 and 3 and by NRPS-6 and 7, respectively. The crossed A domain in NRPS-2 indicates that this deleted domain may be not functional. In model 1, (Figure 9A), (i) the PKS-1 module alone is responsible for the initiation of the acyl-chain assembly, (ii) PKS-4 (HBCL) interacts with PKS-2 and PKS-3 as an AT domain to allow acyl transfer and (iii) NRPS-5 interacts with only NRPS-2. In model 2 (Figure 9B) two different modules, PKS-1 and PKS-4, are responsible for this initiation step. Model 2 leads to the biosynthesis of four different polyketide-polypeptide backbones; in this model (i) PKS-1 (AL) and PKS-4 (HBCL) are in competition for initiation of albicidin precursors; (ii) a separate AT enzyme (potentially AlbXIII) interacts with PKS-2 and PKS-3 to allow acyl transfer; (iii) NRPS-5 interacts with NRPS-2; and (iv) NRPS-5 and NRPS-6 are in competition for interaction with NRPS-4.

Both models are based on the fact that PKS-1 contains the AL and ACP1 domains, and PKS-4 shows homology with the hydroxybenzoate-CoA ligases. In other PKS systems, an N-terminal AL domain is involved in the activation and incorporation of an 3,4-dihydroxycyclo

hexane carboxylic acid, a 3-amino-5-hydroxybenzoic acid or a long-chain fatty acid as a starter (Aparicio *et al.*, 1996; Motamedi and Shafiee, 1998; Tang *et al.*, 1998; Duitman *et al.*, 1999). PKS-4 may be also involved in the activation and incorporation of hydroxy-benzoate but this latter domain lacks any ACP or PCP domain, suggesting that PKS-4 is responsible for initiation of the acyl-chain assembly (Figure 9B) onto one of the three ACP domains of AlbI (ACP1, ACP2 or ACP3). The 277 amino-acids preceding the PKS-4 module in AlbVII may be necessary for the intercommunication between AlbVII and AlbI. The presence of two different PKS modules potentially involved in the initiation of the acyl-chain assembly suggests a competition of these two modules for the initiation of two different albicidin polyketide-polypeptide backbones, and this could contribute to the production of multiple, structurally related albicidins by the same cluster XALB1. Production of two different components, one initiated by PKS-4 containing an additional aromatic ring due to incorporation of hydroxybenzoate, may explain why partial characterization of albicidin indicated the presence of a variable number (three or four) of aromatic rings (Huang *et al.*, 2001).

In AlbI, PKS-1 is followed by the PKS-2 module which contains a KS domain and a KR domain upstream from two ACP domains (ACP2 and ACP3) and it lacks any discernable AT domain. Tandem ACP domains are unusual within PKS modules but have been shown to occur in the biosynthesis of several fungal and bacterial polyketide synthases (Mayorga and Timberlake, 1992; Yu and Leonard, 1995; Takano *et al.*, 1995; Albertini *et al.*, 1995). However, the significance of the tandem ACP domains in these systems has not been solved yet. In our model 2, one of the tandem ACP (ACP2 or ACP3) may interact with PKS-4 for the initiation of an acyl-chain assembly (Figure 9B). The absence of an AT domain in the PKS-2 module suggests that a separate AT domain is indispensable for the elongation of the acyl-chain initiated by this module. Separate AT enzymes encoded elsewhere in the genome were described in other systems for two PKS modules lacking AT domains: malonyl-CoA transacyclase gene (*fenF*) located immediately upstream from the *B. subtilis* PKS-NRPS *mycA* gene (Duitman *et al.*, 1999) and an AT gene located 20kb upstream from the *M. xanthus* NRPS-PKS *tal* gene (Paitan *et al.*, 1999). We have not identified an AT gene in the gene cluster XALB1 and in the two other genomic regions involved in albicidin production, XALB2 and XALB3, suggesting that the *trans*-acting AT gene may be encoded elsewhere in the genome. However, AlbXIII, which contains the motif GHSxG conserved in AT domains, may be potentially involved in the acyl transfer, but the similarity of AlbXIII with AT domains is not high enough to confirm this potential function of AlbXIII (Figure 10). Figure

10A describes alignment of the conserved motifs in AT domains from RifA-1, -2, -3, RifB-1, RifE-1 (Rifamycin PKSs, August *et al.*, 1998) and BlmVIII (Bleomycin PKS; Du *et al.*, 2000), identical amino acids are shown in bold. Figure 10B describes alignment of AlbXIII (SEQ ID N°. 38), FenF (a malonyl-CoA transacylase located upstream from *mycA*, Duitman *et al.*, 1999) and LipA (a lipase; Valdez *et al.*, 1999); amino acids identical to conserved AT domains motifs are shown in bold.

AlbXIII contains only four of the eleven amino acids conserved in AT domains of rifamycin PKSs (August *et al.*, 1998) and Bleomycin PKS (Du *et al.*, 2000), and the AlbXIII sequence appears to be more closely related to lipases such as LipA (Valdez *et al.*, 1999) rather than to AT domains (Figure 10). However, FenF, the *trans*-acting AT domain involved in mycosubtilin biosynthesis, contains only seven of the eleven amino acids conserved in AT domains (Duitman *et al.*, 1999; Figure 10). AlbVII, that contains a HBCL domain, may be another candidate for the acyl transfer in PKS-2 (Figure 9A) because HBCL exhibits some similarity with A domains at the level of cores A1, A2, A3, A4, A5 and A6 (Table 6). However, no HBCL involved in such a function has been described in the PKSs characterized so far.

In AlbI, PKS-2 is followed by the PKS-3 module which contains the KS2 and the PCP1 domains and it lacks any discernable AT or A domain. PKS-3 is located upstream from the NRPS modules and should therefore be involved in the linkage of polyketide and polypeptide moieties. The presence of a PCP domain in the PKS-3 module suggests the involvement of a *trans*-acting A domain rather than an AT domain. A putative candidate for this *trans*-acting A domain is the AlbIV NRPS-5 A domain because of the lack of a C domain in the AlbIV NRPS-5 module. However, by analogy with the BlmVIII PKS module, which is involved in the linkage of polypeptide and polyketide moieties of bleomycin and which contains an AT domain followed by a PCP domain (Du *et al.*, 2000), the presence of a PCP is not incompatible with a possible interaction of the AlbI PKS-3 module with a separate AT domain. This latter *trans*-acting AT domain may be the same that interacts with the AlbI PKS-2 module, the AlbVII PKS-4 module, AlbXIII or an unidentified separate AT domain.

In AlbI, the PKS-3 module is followed by four NRPS modules. The NRPS-1, 2 and 3 modules display the ordered C, A and PCP domains, suggesting that they are involved in the incorporation of three amino acid residues. The A domain of the NRPS-2 module exhibits poor consensus at A2, A3, A5, A7, A8 A9 and A10 motifs and lacks completely the A6 motif (Table 6). In addition the NRPS-2 substrate binding pocket is partially deleted (Figure 5). These features strongly suggest that the NRPS-2 A domain is inactive and that the loading of

an amino-acid on the NRPS-2 PCP domain (PCP3) is possibly catalyzed by a *trans*-acting A domain as in HMWP1 (Gehring *et al.*, 1998) and BlmIII (Du *et al.*, 2000). A putative candidate for this *trans*-acting A domain is the NRPS-5 A domain present in AlbIV because of the lack of a C domain in NRPS-5 (Figure 2). The additional sequence of 300 amino-acids present in the A domain of NRPS-5 may be necessary for the intercommunication between AlbI and AlbIV. As a consequence of the interaction between NRPS-2 and NRPS-5, a competition between PCP-3 and PCP-5 domains must occur to bind the amino acid activated by the NRPS-5 A domain. A similar competition between two PCP domains was described for syringomycin biosynthesis, during the interaction between SyrB, which contains A and PCP domains, and the last module of SyrE which contains C and PCP domains (Guenzi *et al.*, 1998). The NRPS-4 module contains only a C domain which may transfer the intermediate products synthesized by AlbI to a PCP domain present in an other albicidin synthase. Similar transfers were described for mycosubtilin biosynthesis in which the MycA and MycB C-terminal C domains interact with the MycB and MycC N-terminal A domains, respectively (Duitman *et al.*, 1999). Two different PCP domains may be involved in the transfer of the intermediate products synthesized by AlbI: the PCP-5 and PCP-6 domains which are present in the AlbIV NRPS-5 and AlbIX NRPS-6 modules, respectively. This possible competition between the two NRPS modules that contain two different A domains could also contribute to the production of multiple, structurally related albicidins by the gene cluster XALB1 (Figure 9B). Because of the absence of a C-domain in the AlbIX NRPS-6 module, the intermediate product bound on the AlbIV PCP-5 domain would be necessarily transferred to the AlbIX PCP-7 domain, like the intermediate product bound on AlbIX PCP-6. AlbIX NRPS-7, which contains the single chain-terminating TE domain, may then be responsible for detachment of the mature albicidin polyketide-polypeptide backbone from the complex of enzymes.

The linear model 1 implies that operon 1 and operon 2 in *X. albilineans* strain Xa23R1 from Florida potentially produce only one albicidin polyketide-polypeptide backbone, with a competition at the level of ACP2/ACP3 and PCP3 and PCP5 which could explain the production by *X. albilineans* of compounds structurally related to albicidin (Figure 9A). The linear model 2 implies that operon 1 and operon 2 in *X. albilineans* strain Xa23R1 from Florida potentially produce four different albicidin polyketide-polypeptide backbones (Figure 9B) because of (i) the competition of AL and HBCL domains for initiation of acyl chain assembly and (ii) the competition of AlbIV NRPS-5 and AlbIX NRPS-6 modules for the incorporation of the next to last amino acid of the albicidin backbone. These four albicidin backbones may lead to the production of four components structurally very different. The

polyketide moieties of the acyl chains initiated by the AlbI AL domain or by the AlbVII HBCL domain may be very different. The polyketide moiety of acyl chains initiated by the AlbVII HBCL domain may be shorter and may contain an additional aromatic ring. The presence of four structurally different metabolites may explain the difficulty observed by Birch and Patil (1985a) to purify albicidin and to determine its chemical structure.

Homology analysis also revealed that AlbI NRPS-1 and 3 and AlbIX NRPS-6 and 7 specify unusual substrates which seem to contain an amino group and a carboxylate group but to be different from α -amino acids and β -alanine. Identification of several aromatic rings in albicidin (Huang *et al.*, 2001) suggested that NRPS-1, -3, -6 and -7 are involved in incorporation of aromatic substrates. By analogy with the Asp235Val alteration in the β -Ala specificity-conferring code (Du *et al.* 2000), the Asp235Ala alteration in the NRPS-1, -3, -6 and -7 signatures could be consistent with a large distance between the amino group and the carboxylate group in the substrate specified by these modules. Based on this hypothesis, we suggest that operons 3, 4 and 5 are involved in the biosynthesis of two aromatic substrates: the para-aminobenzoate potentially synthesized by AlbXVII (para-aminobenzoate synthase), and the carbamoyl benzoate potentially synthesized by AlbXX (hydroxybenzoate synthase) and AlbXV (carbamoyl transferase). Incorporation of these nonproteinogenic substrates may explain why albicidin is insensitive to proteases (Birch and Patil, 1985a).

According to biosynthesis model 1 leading to the biosynthesis of only one polyketide-polypeptide albicidin backbone that may correspond to the major component produced by XAlb1, we propose a model allowing prediction of the composition and the structure of albicidin (Figure 11). In the Figure, NRPS and PKS domains are abbreviated as follows: A, adenylation; ACP, acyl carrier protein; AL, acyl-CoA ligase; C, condensation; KR, ketoreductase; KS, ketoacyl synthase; PCP, peptidyl carrier protein. C atoms of albicidin backbone are numbered 1 to 38. Bold methyl groups correspond to methylation of the albicidin backbone by AlbII or AlbVI. In this model, albicidin biosynthesis is initiated by loading of an acetyl-CoA by PKS-1 (step 1), and the chain product is elongated by incorporation of (i) malonyl-CoA by PKS-2 and PKS-3 (steps 2 and 3), (ii) para-aminobenzoate or carbamoyl benzoate by NRPS-1 and NRPS-3 (steps 4 and 6), (iii) asparagine by NRPS-2 coupled to NRPS-5 (step 5) and (iv) para-aminobenzoate or carbamoyl benzoate by NRPS-6 and NRPS-7 (steps 7 and 8). The presence of the KR domain in the PKS-2 module may lead to the formation of an hydroxyl group at the C₂ atom of the albicidin backbone. This hydroxyl group might be methylated by AlbVI (*O*-methyltransferase). The acyl chain may also be modified by AlbII (*C*-methyltransferase) at C₁₃ or C₁₄.

The chemical composition ($C_{40}O_{15}N_6H_{35}$), the molecular weight (839), and the structure of the putative XALB1 product are in accordance with the partial characterization of albicidin published by Birch and Patil (1985a) which indicated that albicidin contains approximately 38 carbon atoms and a carboxylate group and that the molecular weight of albicidin was about 842. The presence of two ester linkages in our predicted albicidin structure is also in accordance with the fact that albicidin is detoxified by the AlbD esterase (Zhang and Birch, 1997). However, an unpublished albicidin analysis cited by Huang *et al.* (2001) indicated the presence of (i) two OCH₃ groups and not one as in our predictive albicidin structure, (ii) one CN linkage and not eleven as in our predictive albicidin structure and (iii) a trisubstituted double bond that is not present in the putative XALB1 product. Further investigations to identify the substrate of modules NRPS-1, 3, 6 and 7 and to characterize the structure of albicidin are necessary to valid our model for albicidin biosynthesis.

In conclusion, homology analysis of XALB1 revealed unprecedented features for hybrid polyketide-peptide biosynthesis in bacteria involving a *trans*-action of four PKS and seven NRPS separate modules which could contribute to the production of multiple, structurally related polyketide-peptide compounds by the same gene cluster. Characterization of the full chemical structure of albicidin may be necessary to validate these models. Four NRPS modules seem to activate a very unusual substrate. Over- expression and purification of A domains from these four NRPS modules will be necessary to examine their substrate specificities. Substrate specificity of each A domain will therefore be determined by analysis of the ATP-PPi exchange reaction with different substrate putatively incorporated into albicidin. Investigating albicidin backbone biosynthesis will be of great interest because such information adds to the limited knowledge as to how PKS and NRPS interact and how they might be manipulated to engineer novel molecules, and may explain how *X. albilineans* produces several structurally related, toxic compounds.

Cloning and sequencing of XALB2 showed that the same phosphopantetheinyl transferase is required for albicidin production in an *X. albilineans* strain from Florida and in an *X. albilineans* strain from Australia (Huang *et al.*, 2000b), explaining the precedented results showing that strain LS156 mutated in *xabA* (100% identical to *albXXI*) was not complemented by pALB540, pALB571 and pALB639 (Rott *et al.*, 1996). Mutant LS156 was shown to be complemented by a construction containing the coding sequence of *xabA* in fusion with *lacZ*, revealing that *xabA* is required for albicidin production and that no other cistron downstream from *xabA* was involved in albicidin production (Huang *et al.*, 2000b).

However, this complementation study did not allow determination of whether *xabA* is transcribed as a part of a larger operon. Here we disclose the complementation of mutant AM37 with a 2986 bp insert from *X. albilineans* containing *albXXI* (100% identical to *xabA*), confirming that *albXXI* is involved in albicidin biosynthesis and indicating that the promoter of *albXXI* is present in the 2986 bp insert and that *albXXI* is not expressed as part of a operon.

Cloning and sequencing of XALB3 showed that a heat shock protein HtpG was involved in albicidin production in *X. albilineans*. The heat shock protein HtpG is an *Escherichia coli* homologue of eukaryotic HSP90 molecular chaperone. Hsp90 from eukaryotes has been demonstrated to possess chaperone activity (Jakob *et al.*, 1995), acting as a non-ATP dependent 'holder', and it also has an important role in signal transduction and the cell cycle. This protein is essential in both drosophila and yeast (Borkovich *et al.*, 1989; Cutforth and Rubin, 1994). In contrast, the HtpG gene can be deleted in *E. coli* with no effect on the viability of the strain with the exception of decreased growth rate at high temperatures (Bardwell and Craig, 1988). The *in vivo* role of the HtpG protein remains unknown. However, preliminary results indicated that HtpG facilitates *de novo* protein folding in stressed *E. coli* cells, presumably by expanding the ability of the DnaK-DnaJ-GrpE molecular chaperone system to interact with newly synthesized polypeptides (Thomas and Baneyx, 2000). Furthermore, HtpG was copurified in *E. coli* with MccB17 synthetase, an enzyme involved in the biosynthesis of the peptide antibiotic microcin B17 which inhibits DNA replication by induction of the SOS repair system, suggesting the requirement of HtpG for production of the antibiotic (Li *et al.*, 1996). However, when microcin B17 production by the *E. coli* strain deleted for HtpG was compared to the one of the parental strain, there was no effect on microcin B17 production *in vivo*. This result implied that the copurification of HtpG with the MccB17 synthetase was potentially an artefact, or that another *E. coli* chaperone could substitute for HtpG (Milne *et al.*, 1999). To examine the effect of HtpG on the reconstitution of MccB17 synthetase *in vitro*, the chaperone was expressed and purified as a fusion to a hexahistidine (His₆) tag. Addition of the His₆-HtpG did not stimulate MccB17 synthetase reconstitution or heterocyclisation activity *in vitro*, suggesting that HtpG mediates complex assembly or stabilizes protein subunits prior to the hetero-oligomerisation (Milne *et al.*, 1999). Based on these results, we suggest that the function of AlbXXII is to mediate complex assembly by facilitating *de novo* protein folding of PKS and NRPS enzymes (AlbI, AlbIV, AlbVII and AlbIX) involved in the albicidin backbone biosynthesis.

Characterization of the complete sequence of XALB1, XALB2 and XALB3 clusters enables one to characterize all enzymes of the albicidin biosynthesis pathway including

structural, resistance, secretory and regulatory elements, and to engineer overproduction of albicidin. For example one may insert expression enhancing DNA into the genome of *X. albilineans* in a position operable to enhance expression of the Albicidins Biosynthesis Gene Clusters. One may also modify naturally occurring Albicidins to obtain additional non-naturally occurring antibiotics by adding DNA encoding additional enzymes selected to produce a modified albicidin like molecule. This approach will allow (i) the purification of albicidin and the other compounds structurally related and potentially produced by the same biosynthesis apparatus; (ii) the characterization of chemical structure of albicidin; (iii) the investigation of mode of action of albicidin in the pathogenesis of *X. albilineans* in sugarcane; and (iv) the characterization of the bactericidal activity of albicidin. For example one may also increase the resistance of plants to damage from *X. albilineans* infection by inserting one or more of the resistance genes identified herein into the genome of the plant. One may also provide materials to prevent damage by albicidin produced by *X. albilineans* by applying an agent that blocks expression of the Albicidin Biosynthesis Gene Clusters to the plant to be protected. One may also use portions of the DNA of the Albicidin Biosynthesis Gene Clusters to obtain agents useful in blocking expression of albicidin by screening materials against a modified host cell line that expresses the Albicidin Biosynthesis Gene Clusters and selecting for materials that stop or decrease albicidin production.

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Note: In the sequence listing hereafter <210> = SEQ ID

SEQUENCE LISTING

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 ttgcacagca aatccttcgt cgatgtggcg cgcggcgacc tggacctggg caagctggac 1500
 20 agcgaagaag aaaagcaggc gcaggaagaa gccgccaagg ccaagcaagg gctggccgag 1560
 cgcaccagc aggtactcaa ggacgaggtc gccgaggtgc gggctctcgca ccggtcgacc 1620
 25 gattcgccgg cgattcttgc catcgccagc ggcgacatgg gtctgcaaat gcggcagatc 1680
 ctggaagcca gcgggcagaa gctgccggag agcaagccgg tgttcgagtt caaccccgcg 1740
 catccgctga tcgagaaact ggatgcggaa cccgatgtcg atcgtttcgg tgatctggcg 1800
 30 cgggtgctgt tcgatcaggc cgcgctggcc gccggcgaca gcctcaagga cccggccgcc 1860
 tacgtgcgtc ggctcaacaa gctgttgctg gagctgtcgg cgtaa 1905
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 <210> 26
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 <213> Xanthomonas albilineans
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 <400> 26

	Met	Pro	Asn	Ala	Leu	Met	Gln	Ile	Thr	Leu	Val	Ala	Val	Gln	Phe	Ala	
	1				5					10						15	
5	Gly	Val	Leu	Leu	Gly	Val	Thr	Ala	Arg	Ala	Ala	Ile	Pro	Asn	Lys	Ala	
				20					25					30			
10	Gly	Met	Arg	Arg	Ala	Trp	Pro	Pro	Phe	Pro	Gln	Ala	Cys	Cys	Arg	Ser	
		35						40					45				
15	Ile	Ala	Tyr	Leu	Met	Gln	Arg	Ser	Pro	Met	Ser	Pro	Leu	Gln	Gln	Thr	
	50						55					60					
20	Leu	Leu	Thr	Arg	Leu	Ala	Ser	Ala	Ala	Ala	Ser	Arg	Thr	Met	Ile	Glu	
	65					70					75					80	
25	Phe	Pro	Arg	Pro	Glu	His	Ala	Ser	Pro	Gln	Cys	Cys	Asp	Asp	Ala	Glu	
					85					90					95		
30	Leu	Ala	Arg	Leu	Ile	Val	Gln	Leu	Ser	Ala	Gly	Leu	Gln	Pro	Leu	Ala	
				100					105					110			
35	Met	Pro	Gly	Thr	Tyr	Val	Ile	Ile	Ala	Ala	Pro	His	Gly	Gly	Leu	Phe	
		115						120					125				
40	Ala	Ala	Ala	Leu	Leu	Ala	Cys	Leu	His	Ala	Asn	Leu	Val	Ala	Val	Pro	
		130					135					140					
45	Phe	Pro	Leu	Asp	Val	Ala	Gln	Pro	Asn	Glu	Arg	Glu	Gln	Ala	Arg	Leu	
	145					150				155						160	
50	Glu	Thr	Ile	His	Ala	Gln	Leu	Met	Glu	His	Gly	Asn	Val	Ala	Val	Leu	

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Application of Royer, et al.

165

170

175

5 Leu Asp Asp Val Ala Asp Arg Ser Ala Phe Ala Arg Met Ala His Ala
180 185 190

10 Ala Gly Thr Phe Leu Ala Thr Phe Ala Asp Leu Lys Arg Glu Ser Thr
195 200 205

15 Ser Ala Ser Leu Cys Pro Ala Ser Pro Ser Asp Ala Ala Leu Leu Leu
210 215 220

Phe Thr Ser Gly Ser Ser Gly Glu Ser Lys Gly Ile Leu Leu Ser His
225 230 235 240

20 Arg Asn Leu His His Gln Ile Gln Ala Gly Ile Arg Gln Trp Ser Leu
245 250 255

25 Asp Glu His Ser His Val Val Thr Trp Leu Ser Pro Ala His Asn Phe
260 265 270

30 Gly Leu His Phe Gly Leu Leu Ala Pro Trp Phe Ser Gly Ala Thr Val
275 280 285

Ser Phe Ile His Pro His Ser Tyr Met Lys Arg Pro Gly Phe Trp Leu
290 295 300

35 Glu Thr Val Ala Ala Arg Asp Ala Thr His Met Ala Ala Pro Asn Phe
305 310 315 320

40 Ala Phe Asp Tyr Cys Cys Asp Trp Val Met Val Glu Gln Leu Pro Pro
325 330 335

5

Ser Ala Leu Ser Thr Leu Thr His Ile Val Cys Gly Gly Glu Pro Val
340 345 350

10

Arg Ala Ser Thr Met Gln Arg Phe Phe Glu Lys Phe Ala Gly Leu Gly
355 360 365

15

Ala Arg Thr Gln Thr Phe Met Pro His Phe Gly Leu Ser Glu Thr Gly
370 375 380

Ala Leu Ser Thr Leu Asp Glu Ala Pro Gln Gln Arg Val Leu Glu Leu
385 390 395 400

20

Asp Ala Asp Ala Leu Asn Lys Arg Lys Arg Val Ala Ala Gly Ala Ser
405 410 415

Gln Ala Arg Val Thr Val Leu Asn Cys Gly Ala Val Asp Gln Asp Val
420 425 430

25

Glu Leu Arg Ile Val Cys Pro Glu Gly Glu Thr Leu Cys Arg Pro Asp
435 440 445

30

Glu Ile Gly Glu Ile Trp Val Lys Ser Pro Ala Ile Ala Arg Gly Tyr
450 455 460

35

Leu Phe Ala Lys Pro Ala Asp Gln Arg Gln Phe Asn Cys Ser Ile Arg
465 470 475 480

40

His Thr Asp Asp Ser Gly Tyr Phe Arg Thr Gly Asp Leu Gly Phe Ile
485 490 495

Ala Asp Gly Cys Leu Tyr Val Thr Gly Arg Val Lys Glu Val Leu Ile
500 505 510

5 Ile Arg Gly Lys Asn His Tyr Pro Ala His Ile Glu Ala Ser Ile Ala
515 520 525

10 Ala Thr Ala Ser Pro Gly Ala Leu Met Pro Val Val Phe Ser Ile Glu
530 535 540

15 Arg Gln Asp Glu Glu Arg Val Ala Ala Val Ile Ala Val Asn His Pro
545 550 555 560

Trp Thr Pro Ala Ala Cys Ala Ala Gln Ala His Lys Ile Arg Gln Gln
565 570 575

20 Val Ala Asp Gln His Gly Val Ala Leu Ala Glu Leu Ala Phe Ala Glu
580 585 590

25 His Arg His Val Phe Gly Thr Tyr Pro Gly Lys Leu Lys Arg Arg Leu
595 600 605

30 Val Lys Glu Ala Tyr Val Asn Gly Gln Leu Pro Leu Leu Trp His Glu
610 615 620

35 Gly Lys Asn Arg Asp Val Pro Ala Ala Ala Ala Asp Asp Arg Gln Ala
625 630 635 640

Gln His Val Ala Asp Leu Cys Arg Lys Val Phe Leu Pro Val Leu Gly
645 650 655

40 Val Ala Pro Pro His Ala Gln Trp Pro Leu Cys Glu Leu Ala Leu Asp

	660	665	670
5	Ser Leu Gln Cys Val Arg Leu Ala Gly Ala Ile Glu Glu Cys Tyr Gly 675 680 685		
10	Val Pro Phe Glu Pro Thr Leu Leu Phe Lys Leu Glu Thr Val Gly Ala 690 695 700		
15	Ile Ala Glu Tyr Val Leu Ala His Gly Arg Gln Ala Pro Thr Pro Thr 705 710 715 720		
20	Arg Ala Pro Val Ala Ser Thr Thr Cys Ser Glu Glu Pro Ile Ala Ile 725 730 735		
25	Val Ala Met His Cys Glu Val Pro Gly Ala Gly Glu Asn Thr Glu Ala 740 745 750		
30	Leu Trp Ser Phe Leu Arg Ser Asp Val Asn Ala Ile Arg Pro Ile Glu 755 760 765		
35	Ser Thr Arg Pro Asp Leu Trp Ala Ala Met Arg Ala Tyr Pro Gly Leu 770 775 780		
40	Ala Gly Glu Gln Leu Pro Arg Tyr Ala Gly Phe Leu Asp Asp Val Asp 785 790 795 800		
	Ala Phe Asp Ala Ala Phe Phe Gly Ile Ser Arg Arg Glu Ala Glu Cys 805 810 815		
	Met Asp Pro Gln Gln Arg Lys Val Leu Glu Met Val Trp Lys Leu Ile 820 825 830		

Glu Gln Ala Gly His Asp Pro Leu Ser Trp Gly Gly Gln Pro Val Gly
835 840 845

5
Leu Phe Val Gly Ala His Thr Ser Asp Tyr Gly Glu Leu Leu Ala Ser
850 855 860

10
Gln Pro Gln Leu Met Ala Gln Cys Gly Ala Tyr Ile Asp Ser Gly Ser
865 870 875 880

15
His Leu Thr Met Ile Pro Asn Arg Ala Ser Arg Trp Phe Asn Phe Thr
885 890 895

20
Gly Pro Ser Glu Val Ile Asn Ser Ala Cys Ser Ser Ser Leu Val Ala
900 905 910

25
Leu Val Leu Gly Val Asn Leu Ile Leu Ala Pro Lys Val Leu Leu Ala
930 935 940

30
Ser Ala Ser Ala Gly Met Leu Ser Pro Asp Gly Arg Cys Lys Thr Leu
945 950 955 960

35
Asp Ala Ala Ala Asp Gly Phe Val Arg Ser Glu Gly Ile Ala Gly Val
965 970 975

40
Ile Leu Lys Pro Leu Ala Gln Ala Leu Ala Asp Gly Asp Arg Val Tyr
980 985 990

	Gly	Leu	Val	Arg	Gly	Val	Ala	Val	Asn	His	Gly	Gly	Arg	Ser	Asn	Ser
	995							1000						1005		
5	Leu	Arg	Ala	Pro	Asn	Val	Asn	Ala	Gln	Arg	Gln	Leu	Leu	Ile	Arg	
	1010						1015					1020				
10	Thr	Tyr	Gln	Glu	Ala	Gly	Val	Glu	Pro	Ala	Ser	Val	Gly	Tyr	Val	
	1025						1030						1035			
15	Glu	Leu	His	Gly	Thr	Gly	Thr	Ser	Leu	Gly	Asp	Pro	Ile	Glu	Ile	
	1040						1045					1050				
20	Gln	Ala	Leu	Lys	Glu	Ala	Phe	Ile	Ala	Leu	Gly	Ala	Gln	Ala	Ala	
	1055						1060					1065				
25	Pro	Ser	Asn	Cys	Gly	Ile	Gly	Ser	Val	Lys	Ser	Ala	Leu	Gly	His	
	1070						1075					1080				
30	Leu	Glu	Ala	Ala	Ala	Gly	Leu	Thr	Gly	Leu	Ile	Lys	Val	Leu	Leu	
	1085						1090					1095				
35	Met	Leu	Lys	His	Gly	Glu	Gln	Ala	Gly	Thr	Arg	His	Phe	Ser	Thr	
	1100						1105					1110				
40	Leu	Asn	Pro	Leu	Ile	Asp	Leu	Arg	Gly	Thr	Ser	Phe	Glu	Val	Val	
	1115						1120					1125				
	Ala	Gln	His	Arg	Ala	Trp	Pro	Ser	Gln	Val	Gly	Ile	His	Gly	Thr	
	1130						1135					1140				
	Leu	Leu	Pro	Arg	Arg	Ala	Gly	Ile	Ser	Ser	Phe	Gly	Phe	Gly	Gly	

	1145		1150		1155	
5	Ala Asn 1160	Ala His 1160	Ala Ile 1165	Val Glu 1165	Glu Glu His Val Ile 1170	Ala Thr Pro 1170
10	Pro Ser 1175	Thr Ser 1175	Ser Ala 1180	Gly Gly 1180	Pro Val Gly Ile 1185	Val Leu Ser 1185
15	Ala Gly 1190	Ser Glu 1190	Ala Val 1195	Leu Arg 1195	Gln Gln Val Leu 1200	Ala Leu Ser 1200
20	Ala Trp 1205	Leu Arg 1205	Gln Gln 1210	Ser Pro 1210	Thr Pro Ala Gln 1215	Met Ile Asp 1215
25	Val Ala 1220	Tyr Thr 1220	Leu Gln 1225	Val Gly 1225	Arg Ala Ala Leu 1230	Ser His Arg 1230
30	Leu Ala 1235	Phe Ser 1235	Ala Thr 1240	Asp Ala 1240	Glu Gln Ala Leu 1245	Ala Arg Leu 1245
35	Glu Gly 1250	Arg Leu 1250	Ala Gly 1255	Val Met 1255	Asp Ala Glu Val 1260	His His Gly 1260
40	Val Val 1265	Asp Ala 1265	Ala Ala 1270	Thr Ala 1270	Pro Glu His Gly 1275	Arg Gln Thr 1275
45	Arg Glu 1280	Gly Leu 1280	Ala Gly 1285	Leu Leu 1285	Arg Ala Trp Thr 1290	Gln Gly Val 1290
50	Arg Val 1295	Asp Trp 1295	Ser Ala 1300	Leu Tyr 1300	Gly Ile Gln Arg 1305	Pro Gln Arg 1305

	Val	Ser	Leu	Pro	Val	Tyr	Pro	Phe	Ala	Arg	Glu	Arg	Tyr	Trp	Leu
	1310						1315					1320			
5															
	Pro	Gly	Gln	Ala	Met	His	Ala	Ala	Ala	Asp	Ala	His	Pro	Met	Leu
	1325						1330					1335			
10															
	Gln	Leu	Leu	His	Ala	Asn	Ala	Lys	Leu	His	Arg	Tyr	Ala	Leu	Arg
	1340						1345					1350			
15															
	Arg	Ser	Gly	Cys	Ala	Ser	Phe	Leu	Val	Asp	His	Cys	Val	Asp	Gly
	1355						1360					1365			
20															
	Arg	Gln	Val	Leu	Pro	Ala	Ala	Val	Gln	Leu	Glu	Leu	Val	Arg	Ala
	1370						1375					1380			
25															
	Val	Ala	Gln	Arg	Val	Met	Ala	Gln	Asp	Glu	Gly	Cys	Ile	Glu	Leu
	1385						1390					1395			
30															
	Ala	Gln	Val	Ala	Phe	Leu	His	Pro	Leu	Met	Met	Glu	Glu	Thr	Glu
	1400						1405					1410			
35															
	Leu	Glu	Val	Glu	Ile	Glu	Leu	Ser	Lys	Ser	Asp	Gln	Asp	Glu	Phe
	1415						1420					1425			
40															
	Asp	Phe	Gln	Leu	His	Asp	Ala	His	Arg	Gln	Gln	Val	Phe	Ser	Gln
	1430						1435					1440			
45															
	Gly	His	Val	Arg	Arg	Arg	Val	Tyr	Thr	Ala	Thr	Pro	Arg	Leu	Asp
	1445						1450					1455			

	Leu	Ala	Gln	Leu	Gln	Lys	Leu	Cys	Ala	Glu	Arg	Val	Leu	Ser	Gly
	1460						1465						1470		
5	Glu	Asp	Cys	Tyr	Ala	His	Phe	Thr	Ala	Cys	Gly	Leu	Gln	Leu	Gly
	1475						1480						1485		
10	Asp	Arg	Leu	Lys	Ser	Val	Gln	Ser	Ile	Gly	Cys	Gly	Arg	Asn	Gly
	1490						1495						1500		
15	Glu	Gly	Glu	Pro	Ile	Ala	Leu	Gly	Val	Leu	Arg	Leu	Pro	Pro	Ser
	1505						1510						1515		
20	Ser	Val	Glu	Asp	Ser	His	Val	Leu	Pro	Pro	Ser	Leu	Leu	Asp	Gly
	1520						1525						1530		
25	Ala	Leu	Gln	Cys	Ser	Leu	Gly	Leu	Gln	Arg	Asp	Val	Glu	His	Ile
	1535						1540						1545		
30	Ala	Met	Pro	Tyr	Thr	Leu	Glu	Arg	Met	Thr	Val	His	Ala	Pro	Ile
	1550						1555						1560		
35	Pro	Pro	Glu	Ala	Trp	Val	Leu	Leu	Arg	His	Gly	His	Ala	Ala	Arg
	1565						1570						1575		
40	Gln	Ser	Leu	Asp	Ile	Asp	Leu	Leu	Asp	Ser	Glu	Gly	Arg	Val	Cys
	1580						1585						1590		
45	Val	Ser	Leu	Gly	Asn	Tyr	Thr	Gly	Arg	Ala	Pro	Lys	Ala	Val	Ser
	1595						1600						1605		
50	Ala	Val	Arg	Ala	Leu	Val	Leu	Ala	Pro	Val	Trp	Gln	Ala	Leu	Thr

	1610		1615		1620			
5	Glu Thr	Ala Pro	Ala Trp	Pro Asp	Pro Ala	Glu Arg	Ile Val	Thr
	1625			1630			1635	
10	Val Gly	Asp Asp	Ala Trp	Arg Ser	His Phe	Gly Phe	Asp Glu	Pro
	1640			1645			1650	
15	Ala Leu	Ser Leu	Glu Asp	Ser Val	Glu Val	Ile Ala	Thr Arg	Leu
	1655			1660			1665	
20	Gly Gln	Ser Gly	Lys Phe	Asp His	Leu Val	Trp Ile	Val Pro	Ile
	1670			1675			1680	
25	Ala Glu	Ser Glu	Thr Asp	Ile Ala	Ala Gln	Gly Ser	Ala Ala	Ile
	1685			1690			1695	
30	Ala Gly	Phe Arg	Leu Val	Lys Ala	Leu Leu	Ala Leu	Gly Tyr	Ala
	1700			1705			1710	
35	His Arg	Pro Leu	Gly Leu	Thr Val	Leu Thr	Arg Gln	Ala Leu	Thr
	1715			1720			1725	
40	Arg Gln	Pro Ser	His Ala	Ala Val	His Gly	Leu Ile	Gly Thr	Leu
	1730			1735			1740	
45	Ala Lys	Glu Tyr	Cys Asn	Trp Lys	Ile Arg	Leu Leu	Asp Leu	Pro
	1745			1750			1755	
50	Ser Val	Lys Ser	Trp Pro	Gln Trp	Glu Gln	Leu Arg	Ser Leu	Pro
	1760			1765			1770	

	Trp His	Ala Gln Gly Glu Ala	Leu Ile Gly Arg Gly	Thr Cys Trp
	1775		1780	1785
5	Tyr Arg	Arg Gln Leu Cys Glu	Val Leu Pro Leu Pro	Ser Leu Glu
	1790		1795	1800
10	Pro Pro	Pro Tyr Arg Val Gly	Gly Val Tyr Val Val	Ile Gly Gly
	1805		1810	1815
15	Ala Gly	Gly Leu Gly Glu Val	Leu Ser Glu His Leu	Ile Arg Thr
	1820		1825	1830
20	Tyr Asp	Ala Gln Leu Ile Trp	Ile Gly Arg Arg Val	Leu Asp Glu
	1835		1840	1845
	Gly Ile	Ala Arg Lys Gln Thr	Arg Leu Ala Ser Leu	Gly Arg Ala
	1850		1855	1860
25	Pro His	Tyr Ile Ser Ala Asp	Ala Ser Asp Pro Ala	Ala Leu Gln
	1865		1870	1875
30	Ala Ala	His Asn Glu Ile Val	Ala Leu His Gly Gln	Pro His Gly
	1880		1885	1890
35	Leu Ile	Leu Ser Asn Ile Val	Leu Lys Asp Ala Ser	Leu Ala Arg
	1895		1900	1905
40	Met Glu	Glu Ala Asp Phe Arg	Asp Val Leu Ala Ala	Lys Leu Asp
	1910		1915	1920

	Val Ser	Val Cys	Ala Ala	Gln	Val Phe	Gly Thr	Ala	Pro Leu	Asp
	1925			1930				1935	
5	Phe Val	Leu Phe	Phe Ser	Ser	Ile Gln	Ser Thr	Thr	Lys Ala	Ala
	1940			1945				1950	
10	Gly Gln	Gly Asn	Tyr Ala	Ala	Gly Cys	Cys Tyr	Val	Asp Ala	Phe
	1955			1960				1965	
15	Gly Glu	Leu Trp	Ala Arg	Arg	Gly Leu	Arg Val	Lys	Thr Ile	Asn
	1970			1975				1980	
	Trp Gly	Tyr Trp	Gly Ser	Val	Gly Val	Val Ala	Gly	Glu Asp	Tyr
	1985			1990				1995	
20	Arg Arg	Arg Met	Ala Gln	Lys	His Met	Ala Ser	Ile	Glu Gly	Ala
	2000			2005				2010	
25	Glu Ala	Met Gln	Val Leu	Ser	Gln Leu	Leu Cys	Ala	Pro Leu	Gln
	2015			2020				2025	
30	Arg Leu	Ala Tyr	Val Lys	Ile	Asp Asp	Ala Asn	Ala	Met Arg	Ala
	2030			2035				2040	
35	Leu Gly	Val Val	Glu Asp	Glu	Ser Val	Gln Ile	Pro	Val His	Ala
	2045			2050				2055	
40	Pro Ala	Glu Pro	Pro Arg	Gly	Gln Pro	Gly Pro	Val	Val Glu	Leu
	2060			2065				2070	
	Ser Val	Asn Leu	Asp Ala	Arg	Arg Glu	Arg Glu	Thr	Leu Leu	Ala

	2075	2080	2085
5	Ala Trp Leu Leu Glu Leu Ile 2090	Glu Gln Leu Gly Gly 2095	Phe Pro Pro 2100
10	Ala Ser Phe Asp Ile Ala Thr 2105	Leu Ala Gln Arg Leu 2110	His Ile Val 2115
15	Pro Ala Tyr Arg Ser Trp Leu 2120	Glu His Ser Val Arg 2125	Met Leu Gly 2130
20	Val Tyr Gly Tyr Leu Arg Ala 2135	Thr Gly Glu Ser Arg 2140	Phe Glu Leu 2145
25	Ala Asp Lys Pro Pro Asp Asp 2150	Ala Arg Gly Ala Trp 2155	Asn Ala His 2160
30	Val His Glu Ala Ser Val Glu 2165	Ala Gly Glu Glu Ala 2170	Gln Arg Arg 2175
35	Leu Leu Asp Arg Cys Met Arg 2180	Ala Leu Pro Ala Val 2185	Leu Arg Gly 2190
40	Glu Arg Lys Ala Thr Glu Leu 2195	Leu Phe Pro Glu Gly 2200	Ser Met Ala 2205
	Trp Val Glu Gly Ile Tyr Gln 2210	Asn Asn Pro Leu Ala 2215	Asp Tyr Phe 2220
	Asn Ala Gln Leu Val Thr Arg 2225	Leu Ile Ala Tyr Leu 2230	Arg Arg Arg 2235

	Leu	Glu	Ser	Thr	Pro	Thr	Ala	Arg	Leu	Lys	Leu	Cys	Glu	Ile	Gly
	2240						2245					2250			
5	Ala	Gly	Ser	Gly	Gly	Thr	Thr	Ala	Ser	Val	Leu	Gln	Gln	Leu	Gln
	2255						2260					2265			
10	Ala	Tyr	Gly	Glu	His	Ile	Glu	Glu	Tyr	Leu	Tyr	Thr	Asp	Leu	Ser
	2270						2275					2280			
15	Pro	Val	Phe	Leu	His	His	Ala	Glu	Lys	His	Tyr	Gln	Pro	Arg	Ala
	2285						2290					2295			
20	Pro	Tyr	Leu	Arg	Thr	Ala	Cys	Phe	Asp	Val	Ala	Arg	Ala	Pro	Thr
	2300						2305					2310			
25	Ala	Gln	Ala	Leu	Glu	Ser	Gly	Gly	Tyr	Asp	Val	Val	Ile	Ala	Ala
	2315						2320					2325			
30	Asn	Val	Leu	His	Ala	Thr	Arg	Asp	Ile	Ala	Lys	Thr	Leu	Arg	Asn
	2330						2335					2340			
35	Ala	Lys	Ala	Leu	Leu	Lys	Pro	Gly	Gly	Leu	Leu	Leu	Leu	Asn	Glu
	2345						2350					2355			
40	Val	Ile	Glu	Arg	Ser	Leu	Val	Leu	His	Leu	Thr	Phe	Gly	Leu	Leu
	2360						2365					2370			
	Glu	Ser	Trp	Trp	Leu	Pro	Gln	Asp	Lys	Ile	Leu	Arg	Leu	Ala	Gly
	2375						2380					2385			

	Ser Pro	Leu Leu	Ala Cys	Ala Thr	Trp Arg	Ser Leu	Leu Glu	Ala
	2390			2395		2400		
5	Glu Gly	Phe Ala	Gly Leu	Ser Val	His Arg	Ala Gln	Pro Asp	Ala
	2405			2410		2415		
10	Gly Gln	Ala Ile	Ile Cys	Ala Tyr	Ser Asp	Gly Ile	Val Arg	Gln
	2420			2425		2430		
15	Ala Ser	Thr Ile	Glu Val	Ala Arg	Asn Glu	Lys Val	Thr Val	Pro
	2435			2440		2445		
20	Ser Gln	Pro Ala	Glu Ala	Gly Glu	Ser Pro	Leu Asp	Leu Val	Lys
	2450			2455		2460		
25	Lys Leu	Leu Gly	Arg Ile	Leu Lys	Met Asp	Pro Ala	Thr Leu	Asp
	2465			2470		2475		
30	Thr Ser	His Pro	Leu Glu	Tyr Tyr	Gly Val	Asp Ser	Ile Val	Ala
	2480			2485		2490		
35	Ile Glu	Leu Ala	Met Ala	Leu Arg	Glu Thr	Phe Pro	Gly Phe	Glu
	2495			2500		2505		
40	Val Ser	Glu Leu	Phe Glu	Thr Gln	Ser Ile	Asp Thr	Leu Leu	Gly
	2510			2515		2520		
	Ser Leu	Glu Gln	Ala Pro	Leu Leu	Ala Thr	Leu Thr	Ala Pro	Pro
	2525			2530		2535		
	Gln Gln	Asp Met	Leu Gln	Gln Leu	Lys Gln	Leu Leu	Ala Arg	Thr

	2540		2545		2550
5	Leu Lys 2555	Leu Asp Ile Thr Gln 2560	Ile Asp Thr Ser Lys 2565	Thr Leu Glu	
10	Ser Tyr 2570	Gly Val Asp Ser Ile 2575	Val Ile Ile Glu Leu 2580	Ala Asn Ala	
15	Leu Arg 2585	Glu Arg Tyr Pro Ser 2590	Leu Asp Ala Ser Gln 2595	Leu Met Glu	
20	Thr Leu 2600	Ser Ile Asp Arg Leu 2605	Val Ala Gln Trp Gln 2610	Ala Thr Glu	
25	Pro Ala 2615	Val Pro Ala Glu Pro 2620	Thr Ala Glu Pro Pro 2625	Val Ala Asp	
30	Glu Asp 2630	Ala Ala Ala Ile Ile 2635	Gly Leu Ala Gly Arg 2640	Phe Pro Gly	
35	Ala Asp 2645	Thr Leu Glu Glu Phe 2650	Trp Asn Asn Leu Arg 2655	Asn Gly Gln	
40	Ser Ser 2660	Met Gly Glu Val Pro 2665	Gly Glu Arg Trp Asp 2670	His Gln His	
	Tyr Phe 2675	Asp Ser Glu Arg Gln 2680	Ala Pro Gly Lys Thr 2685	Tyr Ser Arg	
	Trp Gly 2690	Ala Phe Leu Arg Asp 2695	Ile Asp Gly Phe Asp 2700	Ala Ala Phe	

Phe Glu Trp Pro Asp Ser Val Ala Leu Glu Ser Asp Pro Gln Ala
 2705 2710 2715

5

Arg Ile Phe Leu Glu Gln Ala Tyr Ala Gly Ile Glu Asp Ala Gly
 2720 2725 2730

10

Tyr Thr Pro Gly Ser Leu Ser Lys Ser Gln Arg Val Gly Val Phe
 2735 2740 2745

15

Val Gly Val Met Asn Gly Tyr Tyr Ser Gly Gly Ala Arg Phe Trp
 2750 2755 2760

20

Gln Ile Ala Asn Arg Val Ser Tyr Gln Phe Asp Phe Arg Gly Pro
 2765 2770 2775

25

Ser Leu Ala Val Asp Thr Ala Cys Ser Ala Ser Leu Thr Ala Ile
 2780 2785 2790

30

His Leu Ala Leu Glu Ser Leu Arg Ser Gly Ser Cys Glu Val Ala
 2795 2800 2805

35

Leu Ala Gly Gly Val Asn Leu Leu Val Asp Pro Gln Gln Tyr Leu
 2810 2815 2820

40

Asn Leu Ala Gly Ala Ala Met Leu Ser Ala Gly Ala Ser Cys Arg
 2825 2830 2835

Pro Phe Gly Glu Ala Ala Asp Gly Phe Val Ala Gly Glu Ala Cys
 2840 2845 2850

	Gly Val	Val Leu Leu Lys	Pro	Leu Lys Gln Ala Arg	Ala Asp Gly
	2855		2860		2865
5	Asp Val	Ile His Ala Val	Ile	Arg Gly Ser Met	Ile Asn Ala Gly
	2870		2875		2880
10	Gly His	Thr Ser Ala Phe	Ser	Ser Pro Asn Pro	Ala Ala Gln Ala
	2885		2890		2895
15	Glu Val	Val Arg Gln Ala	Leu	Gln Arg Ala Gly	Val Ala Pro Asp
	2900		2905		2910
	Ser Ile	Ser Tyr Ile Glu	Ala	His Gly Thr Gly	Thr Val Leu Gly
	2915		2920		2925
20	Asp Ala	Val Glu Leu Gly	Ala	Leu Asn Lys Val	Phe Asp Lys Arg
	2930		2935		2940
25	Ala Ala	Pro Cys Pro Ile	Gly	Ser Leu Lys Ala	Asn Ile Gly His
	2945		2950		2955
30	Ala Glu	Ser Ala Ala Gly	Ile	Ala Gly Leu Ala	Lys Leu Val Leu
	2960		2965		2970
35	Gln Phe	Arg His Gly Glu	Leu	Val Pro Ser Leu	Asn Ala Phe Pro
	2975		2980		2985
	Leu Asn	Pro Tyr Ile Glu	Phe	Gly Arg Phe Gln	Val Gln Gln Gln
	2990		2995		3000
40	Pro Ala	Pro Trp Pro Arg	Arg	Gly Ala Gln Pro	Arg Arg Ala Gly

	3005		3010		3015
5	Leu Ser 3020	Ala Phe Gly Ala Gly	Gly Ser Asn Ala His	Leu Val Val 3030	
10	Glu Glu 3035	Ala Pro Ala Met Ala	Pro Gly Val Ser Ile	Ser Ala Ser 3045	
15	Ser Pro 3050	Ala Leu Ile Val Leu	Ser Ala Arg Thr Leu	Pro Ala Leu 3060	
20	Gln Gln 3065	Arg Ala Arg Asp Leu	Leu Val Trp Met Gln	Ala Arg Gln 3075	
25	Val Asp 3080	Asp Val Met Leu Ala	Asp Val Ala Tyr Thr	Leu His Leu 3090	
30	Gly Arg 3095	Val Ala Met Glu Gln	Arg Leu Ala Phe Thr	Ala Gly Ser 3105	
35	Ala Ala 3110	Glu Leu Ser Glu Lys	Leu Gln Ala Tyr Leu	Gly His Ala 3120	
40	Ile Arg 3125	Ala Asp Ile Tyr Leu	Ser Glu Asp Thr Pro	Gly Lys Pro 3135	
	Ala Gly 3140	Ala Pro Ile Val Ala	Glu Glu Asp Leu Leu	Thr Leu Met 3150	
	Asp Ala 3155	Trp Ile Glu Lys Gly	Gln Tyr Gly Arg Leu	Leu Glu Tyr 3165	

	Trp Thr	Lys Gly Gln Pro Ile	Asp Trp Asn Lys Leu	Tyr Trp Arg
	3170	3175	3180	
5	Lys Leu	Tyr Ala Asp Gly Arg	Pro Arg Arg Ile Ser	Leu Pro Thr
	3185	3190	3195	
10	Tyr Pro	Phe Glu His Arg Arg	Tyr Trp Gln Thr Pro	Val Pro Gly
	3200	3205	3210	
15	Glu Arg	Ser Leu His Ala Thr	Ala Pro Ala Thr Arg	Glu Thr Val
	3215	3220	3225	
20	Ala Val	Gly Ala Met Pro Asp	Pro Ala Gly Ala Thr	Val Gln Ala
	3230	3235	3240	
25	Arg Leu	Cys Ala Leu Cys Gln	Val Leu Leu Gly Lys	Pro Val Thr
	3245	3250	3255	
30	Ala Gln	Met Asp Phe Phe Ala	Val Gly Gly His Ser	Val Leu Ala
	3260	3265	3270	
35	Ile Gln	Leu Val Ser Arg Ile	Arg Lys Ser Phe Gly	Val Glu Tyr
	3275	3280	3285	
40	Pro Val	Ser Ala Leu Phe Glu	Ser Ala Leu Leu Ser	Asp Met Ala
	3290	3295	3300	
	Arg Gln	Ile Glu Gln Leu Arg	Val Asn Gly Val Ala	Lys Arg Met
	3305	3310	3315	

	Pro Ala	Leu Leu	Pro Ala	Gly	Arg Val	Gly Ala	Ile	Pro Ala	Thr
	3320			3325				3330	
5	Tyr Ala	Gln Glu	Arg Leu	Trp	Leu Val	His Glu	His	Met Ser	Glu
	3335			3340				3345	
10	Gln Arg	Ser Ser	Tyr Asn	Ile	Thr Phe	Ala Met	His	Phe Arg	Gly
	3350			3355				3360	
15	Val Asp	Phe Arg	Ala Glu	Ala	Met Arg	Ala Ala	Leu	Asn Ala	Leu
	3365			3370				3375	
20	Val Val	Arg His	Glu Val	Leu	Arg Thr	Arg Phe	Leu	Ser Glu	Asp
	3380			3385				3390	
25	Gly Gln	Leu Gln	Gln Val	Ile	Ala Ala	Ser Leu	Thr	Leu Glu	Val
	3395			3400				3405	
30	Pro Val	Arg Glu	Met Ser	Val	Glu Glu	Val Asp	Leu	Leu Leu	Ala
	3410			3415				3420	
35	Ala Ser	Thr Arg	Glu Thr	Phe	Asp Leu	Arg Gln	Gly	Pro Leu	Phe
	3425			3430				3435	
40	Lys Ala	Arg Ile	Leu Arg	Val	Ala Ala	Asp His	His	Val Val	Leu
	3440			3445				3450	
	Ser Ser	Ile His	His Ile	Ile	Ser Asp	Gly Trp	Ser	Leu Gly	Val
	3455			3460				3465	
	Phe Asn	Arg Asp	Leu His	Gln	Leu Tyr	Glu Ala	Cys	Leu Arg	Gly

	3470		3475		3480
5	Thr Pro Pro Thr Leu Pro Thr	Leu Ala Val Gln Tyr	Ala Asp Tyr		
	3485	3490	3495		
10	Ala Leu Trp Gln Arg Gln Trp	Glu Leu Ala Ala Pro	Leu Ser Tyr		
	3500	3505	3510		
	Trp Thr Arg Ala Leu Glu Gly	Tyr Asp Asp Gly Leu	Asp Leu Pro		
	3515	3520	3525		
15	Tyr Asp Arg Pro Arg Gly Ala	Thr Arg Ala Trp Arg	Ala Gly Leu		
	3530	3535	3540		
20	Val Lys His Arg Tyr Pro Pro	Gln Leu Ala Gln Gln	Leu Ala Ala		
	3545	3550	3555		
25	Tyr Ser Gln Gln Tyr Gln Ala	Thr Leu Phe Met Ser	Leu Leu Ala		
	3560	3565	3570		
30	Gly Leu Ala Leu Val Leu Gly	Arg Tyr Ala Asp Arg	Lys Asp Val		
	3575	3580	3585		
	Cys Ile Gly Ala Thr Val Ser	Gly Arg Asp Gln Leu	Glu Leu Glu		
	3590	3595	3600		
35	Glu Leu Ile Gly Phe Phe Ile	Asn Ile Leu Pro Leu	Arg Val Asp		
	3605	3610	3615		
40	Leu Ser Gly Asp Pro Cys Leu	Glu Glu Val Leu Leu	Arg Thr Arg		
	3620	3625	3630		

	Gln Val	Val Leu Asp Gly Phe	Ala His Gln Ser Val	Pro Phe Glu
	3635	3640	3645	
5	His Val	Leu Gln Ala Leu Arg	Arg Gln Arg Asp Ser	Ser Gln Ile
	3650	3655	3660	
10	Pro Leu	Val Pro Val Met Leu	Arg His Gln Asn Phe	Pro Thr Gln
	3665	3670	3675	
15	Glu Ile	Gly Asp Trp Pro Glu	Gly Val Arg Leu Thr	Gln Met Glu
	3680	3685	3690	
20	Leu Gly	Leu Asp Arg Ser Thr	Pro Ser Glu Leu Asp	Trp Gln Phe
	3695	3700	3705	
	Tyr Gly	Asp Gly Ser Ser Leu	Glu Leu Thr Leu Glu	Tyr Ala Gln
	3710	3715	3720	
25	Asp Leu	Phe Asp Glu Ala Thr	Val Arg Arg Met Ile	Ala His His
	3725	3730	3735	
30	Gln Gln	Ala Leu Glu Ala Met	Val Ser Arg Pro Gln	Leu Arg Val
	3740	3745	3750	
35	Gly Lys	Trp Asp Met Leu Thr	Ala Glu Glu Arg Arg	Leu Phe Ala
	3755	3760	3765	
40	Ala Leu	Asn Ala Thr Gly Thr	Pro Arg Glu Trp Pro	Ser Leu Ala
	3770	3775	3780	

	Gln Gln Phe Glu Arg Gln Ala Gln Ala Thr Pro Gln Ala Ile Ala	
	3785 3790 3795	
5	Cys Val Ser Asp Gly Gln Ser Trp Ser Tyr Ala Gln Leu Glu Ala	
	3800 3805 3810	
10	Arg Ala Asn Gln Leu Ala Gln Ala Leu Arg Gly Gln Gly Ala Gly	
	3815 3820 3825	
15	Arg Asp Val Arg Val Ala Val Gln Ser Ala Arg Thr Pro Glu Leu	
	3830 3835 3840	
20	Leu Met Ala Leu Leu Ala Ile Phe Lys Ala Gly Ala Cys Tyr Val	
	3845 3850 3855	
25	Pro Ile Asp Pro Ala Tyr Pro Ala Ala Tyr Arg Glu Gln Ile Leu	
	3860 3865 3870	
30	Leu Asp Glu Gln Gly Gln Phe His Asn Pro Arg Trp Arg Glu Gln	
	3890 3895 3900	
35	Ala Pro Thr Pro Leu Gly Leu Arg Glu His Pro Gly Asp Leu Ala	
	3905 3910 3915	
40	Cys Val Met Val Thr Ser Gly Ser Thr Gly Arg Pro Lys Gly Val	
	3920 3925 3930	
	Met Val Pro Tyr Ala Gln Leu Tyr Asn Trp Leu His Ala Gly Trp	

	Tyr Val	Leu Asp Arg Gln Leu	Arg Gln Val Pro Ile	Gly Val Met
	4100	4105	4110	
5	Gly Glu	Leu His Val His Ser	Val Gly Met Ala Arg	Gly Tyr Trp
	4115	4120	4125	
10	Asn Arg	Pro Gly Leu Thr Ala	Ser Arg Phe Ile Ala	His Pro Tyr
	4130	4135	4140	
15	Ser Glu	Glu Pro Gly Thr Arg	Leu Tyr Lys Thr Gly	Asp Met Val
	4145	4150	4155	
20	Arg Arg	Leu Ala Asp Gly Thr	Leu Glu Tyr Leu Gly	Arg Gln Asp
	4160	4165	4170	
	Phe Glu	Val Lys Val Arg Gly	His Arg Val Asp Thr	Arg Gln Val
	4175	4180	4185	
25	Glu Ala	Ala Leu Arg Ala Gln	Pro Ala Val Ala Glu	Ala Val Val
	4190	4195	4200	
30	Ser Gly	His Arg Val Asp Gly	Asp Met Gln Leu Val	Ala Tyr Val
	4205	4210	4215	
35	Val Ala	Arg Glu Gly Gln Ala	Pro Ser Ala Gly Glu	Leu Lys Gln
	4220	4225	4230	
40	Gln Leu	Ser Ala Gln Leu Pro	Thr Tyr Met Leu Pro	Thr Val Tyr
	4235	4240	4245	

	Gln Trp	Leu Glu Gln Leu Pro	Arg Leu Ser Asn Gly	Lys Leu Asp
	4250	4255	4260	
5	Arg Leu	Ala Leu Pro Ala Pro	Gln Ala Val His Ala	Gln Glu Tyr
	4265	4270	4275	
10	Val Ala	Pro Arg Asn Gln Ala	Glu Gln Arg Leu Ala	Ala Leu Phe
	4280	4285	4290	
15	Ala Glu	Val Leu Arg Val Glu	Gln Val Gly Ile His	Asp Asn Phe
	4295	4300	4305	
20	Phe Ala	Leu Gly Gly His Ser	Leu Ser Ala Ser Gln	Leu Ile Ser
	4310	4315	4320	
25	Arg Ile	Ala Arg Asp Met Ala	Ile Asp Leu Pro Leu	Ala Met Leu
	4325	4330	4335	
30	Phe Glu	Leu Pro Thr Val Ala	Gln Leu Ser Glu Ser	Leu Ala Ser
	4340	4345	4350	
35	His Ala	Arg Asp Ser Asp Tyr	Asp Val Ile Pro Ala	Ser Thr Glu
	4355	4360	4365	
40	Glu Ala	Thr Ile Pro Leu Ser	Thr Ala Gln Glu Arg	Met Trp Phe
	4370	4375	4380	
	Leu His	Lys Phe Val Gln Glu	Thr Pro Tyr Asn Thr	Pro Gly Leu
	4385	4390	4395	
	Ala Leu	Leu Gln Gly Glu Leu	Asp Ile Ser Ala Leu	Gln Val Ala

	4400	4405	4410
5	Phe Arg Cys Val Leu Glu Arg His Ala Val Leu Arg Thr His Phe 4415 4420 4425		
10	Val Glu Thr Glu Gln Gln Cys Val Gln Val Ile Gly Ala Ala Glu 4430 4435 4440		
15	Gln Phe Val Leu Gln Leu Arg Ser Ile Arg Asp Glu Ala Asp Leu 4445 4450 4455		
20	His Gly Leu Leu His Thr Ala Val Ser Glu Pro Phe Asp Leu Glu 4460 4465 4470		
25	Arg Glu Leu Pro Leu Arg Ala Leu Leu Tyr Arg Leu Asp Asp Arg 4475 4480 4485		
30	Arg His Tyr Leu Ala Val Val Ile His His Ile Val Phe Asp Gly 4490 4495 4500		
35	Trp Ser Thr Ser Ile Leu Phe Arg Glu Leu Ala Thr His Tyr Ala 4505 4510 4515		
40	Ala Cys Arg His Gly Gln Ser Ala Pro Leu Pro Pro Leu Glu Leu 4520 4525 4530		
	Ser Tyr Ala Asp Tyr Ala Arg Trp Glu Arg Ala Arg Leu Asn Gln 4535 4540 4545		
	Glu Asp Ala Leu Arg Lys Leu Glu Tyr Trp Lys Thr Gln Leu Ala 4550 4555 4560		

	Asp	Ala	Pro	Pro	Leu	Val	Leu	Pro	Thr	Thr	Tyr	Ala	Arg	Pro	Val
	4565						4570					4575			
5															
	Phe	Gln	Asn	Phe	Asn	Gly	Ala	Thr	Val	Ala	Leu	Gln	Ile	Glu	Pro
	4580						4585					4590			
10															
	Pro	Leu	Leu	Gln	Arg	Leu	Gln	Arg	Phe	Ala	Asp	Ala	His	Ser	Phe
	4595						4600					4605			
15															
	Thr	Leu	Tyr	Met	Leu	Leu	Leu	Ala	Ala	Leu	Gly	Val	Val	Leu	Ser
	4610						4615					4620			
20															
	Arg	His	Ala	Arg	Gln	Lys	His	Phe	Cys	Ile	Gly	Ser	Pro	Val	Ala
	4625						4630					4635			
25															
	Asn	Arg	Ala	Arg	Ala	Glu	Leu	His	Gly	Leu	Ile	Gly	Leu	Phe	Val
	4640						4645					4650			
30															
	Asn	Thr	Leu	Ala	Val	Arg	Leu	Asp	Leu	Asp	Gly	Asn	Pro	Ser	Val
	4655						4660					4665			
35															
	Arg	Glu	Leu	Leu	Glu	Arg	Ile	His	Cys	Thr	Thr	Leu	Ala	Ala	Tyr
	4670						4675					4680			
40															
	Glu	His	Gln	Asp	Val	Pro	Phe	Glu	Arg	Ile	Val	Glu	Ser	Leu	Lys
	4685						4690					4695			
45															
	Val	Pro	Arg	Asp	Thr	Ala	Arg	Asn	Pro	Leu	Gly	Gln	Val	Met	Leu
	4700						4705					4710			

	Asn Phe	Gln Asn Met	Pro Met	Ser Ala	Phe Asp	Leu	Asp Gly	Val	
	4715		4720			4725			
5	Gln Val	Gln Val	Leu Pro	Met	His Asn	Gly Thr	Ala	Lys Cys	Glu
	4730		4735				4740		
10	Leu Thr	Phe Asp	Leu Leu	Leu	Asp Gly	Ser Arg	Leu	Ser Gly	Phe
	4745		4750				4755		
15	Val Glu	Tyr Ala	Thr Gly	Leu	Phe Ala	Pro Glu	Trp	Val Gln	Ala
	4760		4765				4770		
	Leu Val	Gln Gln	Phe Lys	Cys	Val Leu	Ala Ala	Leu	Val Glu	Arg
	4775		4780				4785		
20	Pro Glu	Ala Ser	Leu Asn	Asp	Leu Pro	Met Ala	Pro	Asn Glu	Ala
	4790		4795				4800		
25	Gln Pro	Ala Ser	Pro Ala	Leu	Met Lys	His Val	Ala	Pro Ser	Leu
	4805		4810				4815		
30	Pro Asn	Leu Leu	Glu Ala	Met	Ala Ala	Asn Asp	Ala	Ala Arg	Leu
	4820		4825				4830		
35	Ala Leu	Gln Ala	Pro Glu	Gly	Ala Leu	Ser Tyr	Ala	Gln Leu	Ile
	4835		4840				4845		
40	Glu Ala	Ala Asn	Glu Phe	Ala	Trp Arg	Leu Arg	Cys	Glu His	Ala
	4850		4855				4860		
	Gly Pro	Asp Lys	Val Val	Ala	Leu Cys	Leu Ala	Pro	Cys Ser	Ala

	4865	4870	4875
5	Leu Val 4880	Val Ala Leu Leu Ala 4885	Ala Ser Leu Cys Gly Ala Ala Ser 4890
10	Val Leu 4895	Ile Asp Pro Thr Thr 4900	Thr Ala Glu Ala Gln Tyr Asp Gln 4905
15	Leu Phe 4910	Glu Thr Arg Ala Gly 4915	Ile Val Val Thr Cys Ser Ser Leu 4920
20	Leu Glu 4925	Lys Leu Pro Leu Asp 4930	Asp Gln Ala Val Val Leu Ile Asp 4935
25	Glu Gln 4940	Ala Ala Glu Ala Thr 4945	Pro Arg Leu Met His Phe Thr Asp 4950
30	Asp Pro 4955	Ala Leu Pro Ala Met 4960	Leu Tyr Cys Val Cys Asp Glu Lys 4965
35	Gly Arg 4970	Thr Arg Thr Ile Met 4975	Val Glu Ser Gly Ser Leu Ser Ser 4980
40	Arg Leu 4985	Leu Asp Ser Val Gln 4990	Arg Phe Ser Leu Glu Arg Thr Asp 4995
	Arg Phe 5000	Leu Leu Arg Ser Pro 5005	Leu Ser Ala Glu Leu Ala Asn Thr 5010
	Glu Val 5015	Leu Gln Trp Leu Ala 5020	Ala Gly Gly Ser Leu Ser Ile Ala 5025

	Pro Met	His Gly	Asp Phe	Asp	Ala Ala	Ala Trp	Leu	Glu Thr	Leu
	5030			5035			5040		
5									
	Ala Thr	Tyr Ala	Ile Thr	Val	Ala Tyr	Leu Ala	Gln	Val Glu	Leu
	5045			5050			5055		
10									
	Thr Glu	Met Leu	Ala His	Leu	Gln Asn	His Pro	Leu	Glu Arg	Asn
	5060			5065			5070		
15									
	Lys Leu	Ala Gly	Leu Arg	Val	Leu Val	Val His	Gly	Ala Pro	Leu
	5075			5080			5085		
20									
	Pro Ile	Ala Pro	Leu Met	Arg	Leu Asp	Ala Trp	Leu	Arg Glu	Val
	5090			5095			5100		
25									
	Gly Gly	Ser Ala	Arg Ile	Phe	Ala Ala	Tyr Gly	Asn	Ala Glu	Phe
	5105			5110			5115		
30									
	Gly Ala	Glu Ile	Leu Ser	Gln	Asp Val	Ser Ala	Ala	Leu Gln	Ala
	5120			5125			5130		
35									
	Gly Ile	Gly Ala	Gln Tyr	Lys	His Arg	Arg Gly	Leu	Phe Pro	Leu
	5135			5140			5145		
40									
	Gly Ala	Asn Ser	Met Cys	His	Val Val	Gln Ser	Asn	Gly Arg	Ile
	5150			5155			5160		
	Ala Pro	Asp Gly	Met Val	Gly	Glu Leu	Trp Ile	Thr	Gln Pro	Ala
	5165			5170			5175		

	Cys	Leu	Tyr	Lys	Thr	Asp	Ala	Leu	Val	Arg	Arg	Leu	Ala	Asn	Gly
	5180						5185					5190			
5	Gln	Leu	Glu	Trp	Leu	Gly	Ser	Leu	Asp	Val	Gln	Ser	Arg	Ile	Asp
	5195						5200					5205			
10	Asp	Pro	Arg	Ile	Asp	Leu	Cys	Val	Val	Glu	Ala	Gln	Leu	Arg	Leu
	5210						5215					5220			
15	Cys	Glu	Asp	Val	Gly	Glu	Ala	Val	Val	Leu	Tyr	Glu	Pro	Leu	Lys
	5225						5230					5235			
	Arg	Cys	Leu	Val	Ala	Tyr	Leu	Ser	Ala	Arg	Ser	Thr	Ala	Ala	Ile
	5240						5245					5250			
20	Met	Thr	Asp	Glu	Thr	Leu	Ala	Arg	Ile	Arg	Gln	Ala	Leu	Ser	Glu
	5255						5260					5265			
25	Thr	Leu	Pro	Asp	Tyr	Leu	Leu	Pro	Ala	Ile	Trp	Val	Pro	Leu	Ala
	5270						5275					5280			
30	His	Trp	Pro	Arg	Leu	Pro	His	Gly	Arg	Val	Asp	Leu	Gly	Ala	Leu
	5285						5290					5295			
35	Pro	Ala	Pro	Asp	Phe	Asp	Leu	Ala	Arg	His	Glu	Ser	Tyr	Ile	Ala
	5300						5305					5310			
	Pro	Arg	Thr	Ala	Val	Glu	Gln	Ala	Val	Ala	Glu	Ile	Trp	Gln	Arg
	5315						5320					5325			
40	Val	Leu	Lys	Arg	Thr	Gln	Val	Gly	Val	His	Asp	Asn	Phe	Phe	Glu

	5330		5335		5340
5	Leu Gly Gly His Ser Val Leu Ala Ile Gln Leu Val Ser Gly Leu				
	5345		5350		5355
10	Arg Lys Ala Leu Ala Ile Glu Val Pro Val Thr Leu Val Phe Glu				
	5360		5365		5370
15	Ala Pro Ile Leu Gly Ala Leu Ala Arg Gln Ile Ala Pro Leu Leu				
	5375		5380		5385
20	Val Ser Glu Arg Arg Pro Arg Pro Pro Gly Leu Thr Arg Leu Glu				
	5390		5395		5400
25	His Thr Gly Pro Ile Pro Ala Ser Tyr Ala Gln Glu Arg Leu Trp				
	5405		5410		5415
30	Leu Val His Glu His Met Glu Glu Gln Arg Thr Ser Tyr Asn Ile				
	5420		5425		5430
35	Ser Asn Ala Ala His Phe Ile Gly Ala Ala Phe Ser Val Glu Ala				
	5435		5440		5445
40	Met Arg Ala Ala Leu Asn Ala Leu Val Ala Arg His Glu Val Leu				
	5450		5455		5460
45	Arg Thr Arg Phe Leu Ser Glu Asp Gly Gln Leu Gln Gln Val Ile				
	5465		5470		5475
50	Ala Ala Ser Leu Thr Leu Glu Val Pro Val Arg Glu Val Ser Ala				
	5480		5485		5490

	Glu	Glu	Val	Asp	Leu	Leu	Leu	Ala	Ala	Ser	Thr	Arg	Glu	Thr	Phe
	5495						5500					5505			
5	Asp	Leu	Arg	Gln	Gly	Pro	Leu	Phe	Lys	Ala	Arg	Ile	Leu	Arg	Val
	5510						5515					5520			
10	Ala	Ala	Asp	His	His	Val	Val	Leu	Ser	Ser	Ile	His	His	Ile	Ile
	5525						5530					5535			
15	Ser	Asp	Gly	Trp	Ser	Leu	Gly	Val	Phe	Asn	Arg	Asp	Leu	His	Gln
	5540						5545					5550			
20	Leu	Tyr	Glu	Ala	Cys	Leu	Arg	Gly	Thr	Pro	Pro	Thr	Leu	Pro	Thr
	5555						5560					5565			
	Leu	Ala	Val	Gln	Tyr	Ala	Asp	Tyr	Ala	Leu	Trp	Gln	Arg	Gln	Trp
	5570						5575					5580			
25	Glu	Leu	Ala	Ala	Pro	Leu	Ser	Tyr	Trp	Thr	Arg	Ala	Leu	Glu	Gly
	5585						5590					5595			
30	Tyr	Asp	Asp	Gly	Leu	Asp	Leu	Pro	Tyr	Asp	Arg	Pro	Arg	Gly	Ala
	5600						5605					5610			
35	Thr	Arg	Ala	Trp	Arg	Ala	Gly	Leu	Val	Lys	His	Arg	Tyr	Pro	Pro
	5615						5620					5625			
40	Gln	Leu	Ala	Gln	Gln	Leu	Ala	Ala	Tyr	Ser	Gln	Gln	Tyr	Gln	Ala
	5630						5635					5640			

	Thr Leu	Phe Met Ser Leu Leu	Ala Gly Leu Ala Leu	Val Leu Gly
	5645		5650	5655
5	Arg Tyr	Ala Asp Arg Lys Asp	Val Cys Ile Gly Ala	Thr Val Ser
	5660		5665	5670
10	Gly Arg	Asp Gln Leu Glu Leu	Glu Glu Leu Ile Gly	Phe Phe Ile
	5675		5680	5685
15	Asn Ile	Leu Pro Leu Arg Val	Asp Leu Ser Gly Asp	Pro Cys Leu
	5690		5695	5700
	Glu Glu	Val Leu Leu Arg Thr	Arg Gln Val Val Leu	Asp Gly Phe
	5705		5710	5715
20	Ala His	Gln Ser Val Pro Phe	Glu His Val Leu Gln	Ala Leu Arg
	5720		5725	5730
25	Arg Gln	Arg Asp Ser Ser Gln	Ile Pro Leu Val Pro	Val Met Leu
	5735		5740	5745
30	Arg His	Gln Asn Phe Pro Thr	Gln Glu Ile Gly Asp	Trp Pro Glu
	5750		5755	5760
35	Gly Val	Arg Leu Thr Gln Met	Glu Leu Gly Leu Asp	Arg Ser Thr
	5765		5770	5775
	Pro Ser	Glu Leu Asp Trp Gln	Phe Tyr Gly Asp Gly	Ser Ser Leu
	5780		5785	5790
40	Glu Leu	Thr Leu Glu Tyr Ala	Gln Asp Leu Phe Asp	Glu Ala Thr

	5795	5800	5805
5	Val Arg 5810	Arg Met Ile Ala His 5815	His Gln Gln Ala Leu Glu Ala Met 5820
10	Val Ser 5825	Arg Pro Gln Leu Arg 5830	Val Gly Lys Trp Asp Met Leu Thr 5835
15	Ala Glu 5840	Glu Arg Arg Leu Phe 5845	Ala Ala Leu Asn Ala Thr Gly Thr 5850
20	Pro Arg 5855	Glu Trp Pro Ser Leu 5860	Ala Gln Gln Phe Glu Arg Gln Ala 5865
25	Gln Ala 5870	Thr Pro Gln Ala Ile 5875	Ala Cys Val Ser Asp Gly Gln Ser 5880
30	Trp Ser 5885	Tyr Ala Gln Leu Glu 5890	Ala Arg Ala Asn Gln Leu Ala Gln 5895
35	Ala Leu 5900	Arg Gly Gln Gly Ala 5905	Gly Arg Asp Val Arg Val Ala Val 5910
40	Gln Ser 5915	Ala Arg Thr Pro Glu 5920	Leu Leu Met Ala Leu Leu Ala Ile 5925
	Phe Lys 5930	Ala Gly Ala Cys Tyr 5935	Val Pro Ile Asp Pro Ala Tyr Pro 5940
	Ala Ala 5945	Tyr Arg Glu Gln Ile 5950	Leu Ala Glu Val Gln Val Ser Ile 5955

	Val	Leu	Glu	Gln	Gly	Glu	Leu	Ala	Leu	Asp	Glu	Gln	Gly	Gln	Phe
	5960						5965					5970			
5	Arg	Asn	Arg	Arg	Trp	Arg	Glu	Gln	Ala	Pro	Thr	Pro	Leu	Gly	Leu
	5975						5980					5985			
10	Arg	Gly	His	Pro	Gly	Asp	Leu	Ala	Cys	Val	Met	Val	Thr	Ser	Gly
	5990						5995					6000			
15	Ser	Thr	Gly	Arg	Pro	Lys	Gly	Val	Met	Val	Pro	Tyr	Ala	Gln	Leu
	6005						6010					6015			
20	His	Asn	Trp	Leu	His	Ala	Gly	Trp	Gln	Arg	Ser	Ala	Phe	Glu	Ala
	6020						6025					6030			
25	Gly	Glu	Arg	Val	Leu	Gln	Lys	Thr	Ser	Ile	Ala	Phe	Ala	Val	Ser
	6035						6040					6045			
30	Val	Lys	Glu	Leu	Leu	Ser	Gly	Leu	Leu	Ala	Gly	Val	Gly	Gln	Val
	6050						6055					6060			
35	Met	Leu	Pro	Asp	Glu	Gln	Val	Lys	Asp	Ser	Leu	Ala	Leu	Ala	Arg
	6065						6070					6075			
40	Ala	Ile	Glu	Gln	Trp	Gln	Val	Thr	Arg	Leu	Tyr	Leu	Val	Pro	Ser
	6080						6085					6090			
	His	Leu	Gln	Ala	Leu	Leu	Asp	Ala	Thr	Gln	Gly	Arg	Asp	Gly	Leu
	6095						6100					6105			

	Leu His	Ser Leu Arg His Val	Val Thr Ala Gly Glu	Ala Leu Pro
	6110	6115	6120	
5	Ser Ala	Val Gly Glu Ala Val	Arg Val Arg Leu Pro	Gln Val Gln
	6125	6130	6135	
10	Leu Trp	Asn Asn Tyr Gly Cys	Thr Glu Leu Asn Asp	Ala Thr Tyr
	6140	6145	6150	
15	His Arg	Ser Asp Thr Val Ala	Pro Gly Thr Phe Val	Pro Ile Gly
	6155	6160	6165	
	Ala Pro	Ile Ala Asn Thr Glu	Val Tyr Val Leu Asp	Arg Gln Leu
	6170	6175	6180	
20	Arg Gln	Val Pro Ile Gly Val	Met Gly Glu Leu His	Val His Ser
	6185	6190	6195	
25	Val Gly	Met Ala Arg Gly Tyr	Trp Asn Arg Pro Gly	Leu Thr Ala
	6200	6205	6210	
30	Ser Arg	Phe Ile Ala His Pro	Tyr Ser Glu Glu Pro	Gly Thr Arg
	6215	6220	6225	
35	Leu Tyr	Lys Thr Gly Asp Met	Val Arg Arg Leu Ala	Asp Gly Thr
	6230	6235	6240	
	Leu Glu	Tyr Leu Gly Arg Gln	Asp Phe Glu Val Lys	Val Arg Gly
	6245	6250	6255	
40	His Arg	Val Asp Thr Arg Gln	Val Glu Ala Ala Leu	Arg Ala Gln

	6260		6265		6270
5	Pro Ala Val Ala Glu Ala Val Val Ser Gly His Arg Val Asp Gly				
	6275		6280		6285
10	Asp Met Gln Leu Val Ala Tyr Val Val Ala Arg Glu Gly Gln Ala				
	6290		6295		6300
	Pro Ser Ala Gly Glu Leu Lys Gln Gln Leu Ser Ala Gln Leu Pro				
	6305		6310		6315
15	Thr Tyr Met Leu Pro Thr Val Tyr Gln Trp Leu Glu Gln Leu Pro				
	6320		6325		6330
20	Arg Leu Ser Asn Gly Lys Leu Asp Arg Leu Ala Leu Pro Ala Pro				
	6335		6340		6345
25	Gln Val Val His Ala Gln Glu Tyr Val Ala Pro Arg Asn Glu Ala				
	6350		6355		6360
30	Glu Gln Arg Leu Ala Ala Leu Phe Ala Glu Val Leu Arg Val Glu				
	6365		6370		6375
	Gln Val Gly Ile His Asp Asn Phe Phe Ala Leu Gly Gly His Ser				
	6380		6385		6390
35	Leu Ser Ala Ser Gln Leu Ile Ser Arg Ile Arg Gln Ser Phe His				
	6395		6400		6405
40	Val Asp Leu Pro Leu Ser Arg Ile Phe Glu Ala Pro Thr Ile Glu				
	6410		6415		6420

	Gly Leu	Val Arg	Gln Leu	Ala	Leu Pro	Ser Glu	Gly Gly	Val Ala	
	6425			6430			6435		
5	Ser Ile	Ala Arg	Val Ala	Arg	Asn Arg	Thr Ile	Pro	Leu Ser	Leu
	6440			6445			6450		
10	Phe Gln	Glu Arg	Leu Trp	Phe	Val His	Gln His	Met	Pro Glu	Gln
	6455			6460			6465		
15	Arg Thr	Ser Tyr	Asn Gly	Thr	Leu Ala	Leu Arg	Leu	Arg Gly	Pro
	6470			6475			6480		
20	Leu Ser	Val Glu	Ala Met	Arg	Ala Ala	Leu Arg	Ala	Leu Val	Leu
	6485			6490			6495		
	Arg His	Glu Ile	Leu Arg	Thr	Arg Phe	Val Leu	Pro	Thr Gly	Ala
	6500			6505			6510		
25	Ser Glu	Pro Val	Gln Val	Ile	Asp Glu	His Ser	Asp	Phe Gln	Leu
	6515			6520			6525		
30	Ser Val	Gln Leu	Val Glu	Asp	Thr Glu	Ile Ala	Ser	Leu Met	Asp
	6530			6535			6540		
35	Glu Leu	Ala Ser	His Ile	Tyr	Asp Leu	Ala Asn	Gly	Pro Leu	Phe
	6545			6550			6555		
40	Ile Ala	Cys Leu	Leu Gln	Leu	Asp Glu	Gln Glu	His	Val Leu	Leu
	6560			6565			6570		

	Ile Gly	Met His His Leu Ile	Tyr Asp Ala Trp Ser	Gln Phe Thr
	6575	6580	6585	
5	Val Met	Asn Arg Asp Leu Arg	Val Leu Tyr His Arg	His Leu Gly
	6590	6595	6600	
10	Leu Ala	Gly Gly Asp Leu Pro	Glu Leu Pro Ile Gln	Tyr Ala Asp
	6605	6610	6615	
15	Tyr Ala	Ile Trp Gln Arg Ala	Gln Asn Leu Asp Ala	Gln Leu Ala
	6620	6625	6630	
	Tyr Trp	Gln Ala Met Leu His	Asp Tyr Asp Asp Gly	Leu Glu Leu
	6635	6640	6645	
20	Pro Tyr	Asp Tyr Pro Arg Pro	Arg Asn Arg Thr Trp	His Ala Ala
	6650	6655	6660	
25	Val Tyr	Thr His Thr Tyr Pro	Ala Glu Leu Val Gln	Arg Phe Ala
	6665	6670	6675	
30	Gly Phe	Val Gln Ala His Gln	Ser Thr Leu Phe Ile	Gly Leu Leu
	6680	6685	6690	
35	Ala Ser	Phe Ala Val Val Leu	Asn Lys Tyr Thr Gly	Arg Asp Asp
	6695	6700	6705	
	Leu Cys	Ile Gly Thr Thr Thr	Ala Gly Arg Thr His	Leu Glu Leu
	6710	6715	6720	
40	Glu Asn	Leu Ile Gly Phe Phe	Ile Asn Ile Leu Pro	Leu Arg Leu

	6725	6730	6735
5	Arg Leu Asp Gly Asp Pro Asp Val Ala Glu Ile Met Arg Arg Thr 6740	6745	6750
10	Arg Leu Val Ala Met Ser Ala Phe Glu Asn Gln Ala Leu Pro Phe 6755	6760	6765
15	Glu His Leu Leu Asn Ala Leu His Lys Gln Arg Asp Thr Ser Arg 6770	6775	6780
20	Ile Pro Leu Val Pro Val Val Met Arg His Gln Asn Phe Pro Asp 6785	6790	6795
25	Thr Ile Gly Asp Trp Ser Asp Gly Ile Arg Thr Glu Val Ile Gln 6800	6805	6810
30	Arg Asp Leu Arg Ala Thr Pro Asn Glu Met Asp Leu Gln Phe Phe 6815	6820	6825
35	Gly Asp Gly Thr Gly Leu Ser Val Thr Val Glu Tyr Ala Ala Glu 6830	6835	6840
40	Leu Phe Ser Glu Ala Thr Ile Arg Arg Leu Ile His His His Gln 6845	6850	6855
	Leu Val Leu Glu Gln Met Leu Ala Ala His Glu Ser Ala Thr Cys 6860	6865	6870
	Pro Leu Asp Val Ala Asp 6875		

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<211> 343

<212> PRT

5 <213> Xanthomonas albilineans

<400> 27

10 Met Asp Ser Ala Leu Pro Thr Ser Ala Phe Thr Phe Asp Leu Phe Tyr
 1 5 10 15

15 Thr Thr Val Asn Ala Tyr Tyr Arg Thr Ala Ala Val Lys Ala Ala Ile
 20 25 30

20 Glu Leu Gly Leu Phe Asp Val Val Gly Gln Gln Gly Arg Thr Pro Ala
 35 40 45

Ala Ile Ala Glu Ala Cys Gln Ala Ser Pro Arg Gly Ile Arg Ile Leu
 50 55 60

25 Cys Tyr Tyr Leu Val Ser Ile Gly Phe Leu Arg Arg Asn Gly Gly Leu
 65 70 75 80

30 Phe Tyr Ile Asp Arg Asn Met Ala Met Tyr Leu Asp Arg Ser Ser Pro
 85 90 95

35 Gly Tyr Leu Gly Gly Ser Ile Lys Phe Leu Leu Ser Pro Tyr Ile Met
 100 105 110

Ser Ala Phe Thr Asp Leu Thr Ala Val Val Arg Thr Gly Lys Ile Asn
 115 120 125

40 Leu Ala Gln Asp Gly Val Val Ala Pro Asp His Pro Gln Trp Val Glu

	130	135	140
5	Phe Ala Arg Ala Met Ala Pro Met Met Ala Leu Pro Ser Ala Leu Ile 145	150	155 160
10	Ala Asn Met Val Ser Leu Pro Ala Asp Arg Pro Ile Arg Val Leu Asp 165	170	175
15	Val Ala Ala Gly His Gly Leu Phe Gly Ile Ala Phe Ala Gln Arg Phe 180	185	190
20	Arg Gln Ala Glu Val Ser Phe Leu Asp Trp Asp Asn Val Leu Asp Val 195	200	205
25	Ala Arg Glu Asn Ala Gln Ala Ala Lys Val Ala Glu Arg Ala Arg Phe 210	215	220
30	Leu Pro Gly Asn Ala Phe Asp Leu Asp Tyr Gly Ser Gly Tyr Asp Val 225	230	235 240
35	Ile Leu Leu Thr Asn Phe Leu His His Phe Asp Glu Val Asp Gly Glu 245	250	255
40	Arg Ile Leu Ala Lys Thr Arg Asp Ala Leu Asn Asp Asp Gly Met Val 260	265	270
	Ile Thr Phe Glu Phe Ile Ala Asp Glu Glu Arg Ser Ser Pro Pro Leu 275	280	285
	Ala Ala Thr Phe Ser Met Met Met Leu Gly Thr Thr Pro Ala Gly Glu 290	295	300

Ser Tyr Thr Tyr Ser Asp Leu Glu Arg Met Phe Arg His Ala Gly Phe
 305 310 315 320

5

Gly His Val Glu Leu Lys Ser Ile Pro Pro Ala Leu Leu Lys Val Val
 325 330 335

10

Val Ser Arg Lys Arg Ala Pro
 340

15

<210> 28
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 <212> PRT
 <213> Xanthomonas albilineans

20

Met Ile Glu Ser Ala Thr Ser Pro Val Ala Lys Thr Glu Arg Ile Trp
 1 5 10 15

25

Cys Thr Glu Leu Asp Leu Asp Ala Leu Asn Ala Met Ser Ala Asn Thr
 20 25 30

30

Met Gln Ala Leu Leu Gly Ile Arg Met Ile Glu Ile Gly Ser Asp Tyr
 35 40 45

35

Leu Val Ser Cys Met Ser Val Asp Trp Arg Cys His Gln Pro Tyr Gly
 50 55 60

40

Val Leu His Gly Gly Ala Ser Val Thr Leu Ala Glu Ala Thr Gly Ser
 65 70 75 80

Met Ala Ala Ser Met Cys Val Pro Ala Gly Gln Arg Cys Val Gly Leu

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85

90

95

5 Asp Ile Asn Ala Asn His Ile Ala Ser Ile Ser Ser Gly Gln Val Gln
100 105 110

10 Cys Ile Ala Arg Pro Leu His Ile Gly Ala Leu Thr Gln Val Trp Gln
115 120 125

15 Met Arg Ile Tyr Asp Glu Gly Asp Arg Thr Ile Cys Val Ser Arg Leu
130 135 140

Thr Met Ala Val Leu Ser Val His Val Ala Arg Val Ser Pro Asn Pro
145 150 155 160

20 Ala Ser Ser Gly Val Gln Thr
165

25 <210> 29
<211> 941
<212> PRT
<213> Xanthomonas albilineans

30 <400> 29

Met Asn Glu Thr Ala Thr Val Thr Lys Ala Thr Leu Ser Ser Ala Lys
1 5 10 15

35 Ala Ser Ile Thr Pro Ala Cys Val His Gln Trp Phe Glu Ala Gln Val
20 25 30

40 Ser Ser Thr Pro Asp Ala Pro Ala Ala Phe Leu Gly Glu Arg Arg Met
35 40 45

	Ser	Tyr	Gly	Gln	Leu	Asn	Thr	Arg	Ala	Asn	Arg	Leu	Ala	Arg	Leu	Leu	
	50						55					60					
5	Gln	Ser	Gln	Gly	Val	Gly	Pro	Gly	Ala	Arg	Val	Ala	Val	Trp	Met	Asn	
	65					70					75					80	
10	Arg	Ser	Pro	Glu	Cys	Leu	Ala	Ala	Leu	Leu	Ala	Val	Met	Lys	Ala	Gly	
					85					90					95		
15	Ala	Ala	Tyr	Val	Pro	Ile	Asp	Leu	Ser	Leu	Pro	Ile	Arg	Arg	Val	Gln	
				100					105						110		
20	Tyr	Ile	Leu	Gln	Asp	Ser	Gln	Ala	Arg	Leu	Val	Leu	Val	Asp	Asp	Glu	
		115						120					125				
25	Gly	Gln	Gly	Arg	Leu	Asp	Glu	Leu	Glu	Leu	Gly	Ala	Met	Thr	Ala	Val	
	130						135					140					
30	Asp	Val	Cys	Gly	Thr	Leu	Asp	Gly	Asp	Glu	Ala	Asn	Leu	Asp	Leu	Pro	
	145					150					155					160	
35	Cys	Asp	Pro	Ala	Gln	Pro	Val	Tyr	Cys	Ile	Tyr	Thr	Ser	Gly	Ser	Thr	
					165					170					175		
40	Gly	Ser	Pro	Lys	Gly	Val	Leu	Val	Arg	His	Ser	Gly	Leu	Ala	Asn	Tyr	
				180					185					190			
45	Val	Ala	Trp	Ala	Lys	Arg	Gln	Tyr	Val	Thr	Ala	Asp	Thr	Thr	Ser	Phe	
		195						200					205				
50	Ala	Phe	Tyr	Ser	Ser	Leu	Ser	Phe	Asp	Leu	Thr	Val	Thr	Ser	Ile	Tyr	

	210	215	220
5	Val Pro Leu Val Ala Gly Leu Cys Val His Val Tyr Pro Glu Gln Gly 225 230 235 240		
10	Asp Asp Val Pro Val Ile Asn Arg Val Leu Asp Asp Asn Gln Val Asp 245 250 255		
15	Val Ile Lys Leu Thr Pro Ser His Met Leu Met Leu Arg Asn Ala Ala 260 265 270		
20	Leu Ala Thr Ser Arg Leu Lys Thr Leu Ile Val Gly Gly Glu Asp Leu 275 280 285		
25	Lys Ala Ala Val Ala Tyr Asp Ile His Gln Arg Phe Arg Arg Asp Val 290 295 300		
30	Ala Ile Tyr Asn Glu Tyr Gly Pro Thr Glu Thr Val Val Gly Cys Ala 305 310 315 320		
35	Ile His Arg Tyr Asp Pro Ala Thr Glu Arg Glu Gly Ser Val Pro Ile 325 330 335		
40	Gly Val Pro Ile Asp His Thr Ser Leu His Leu Leu Asp Glu Arg Leu 340 345 350		
45	Gln Pro Val Ala Pro Gly Glu Val Gly Gln Ile His Ile Gly Gly Ala 355 360 365		
50	Gly Val Ala Ile Gly Tyr Val Asn Lys Pro Glu Ile Thr Asp Ala Gln 370 375 380		

Phe Ile Asp Asn Pro Phe Glu Gly Ser Gly Arg Leu Tyr Ala Ser Gly
 385 390 395 400

5

Asp Leu Gly Arg Met Arg Ala Asp Gly Lys Leu Glu Phe Leu Gly Arg
 405 410 415

10

Lys Asp Ser Gln Ile Lys Leu Arg Gly Tyr Arg Ile Glu Leu Gly Glu
 420 425 430

15

Ile Glu Asn Val Leu Leu Gly His Ala Ala Leu Arg Glu Cys Ile Val
 435 440 445

20

Asp Thr Thr Val Ala Pro Arg Arg Asp Tyr Asp Ser Lys Ser Leu Arg
 450 455 460

25

Tyr Cys Ala Arg Cys Gly Ile Ala Ser Asn Phe Pro Asn Thr Ser Phe
 465 470 475 480

30

Asp Glu His Gly Val Cys Asn His Cys His Ala Tyr Asp Lys Tyr Arg
 485 490 495

35

Asn Val Val Glu Asp Tyr Phe Arg Thr Glu Asp Glu Leu Arg Thr Ile
 500 505 510

40

Phe Glu Gln Val Lys Ala His Asn Arg Leu Arg Tyr Asp Cys Leu Val
 515 520 525

Ala Phe Ser Gly Gly Lys Asp Ser Thr Tyr Ala Leu Cys Arg Val Val
 530 535 540

Asp Met Gly Leu Arg Val Leu Ala Tyr Thr Leu Asp Asn Gly Tyr Ile
 545 550 555 560

5 Ser Asp Glu Ala Lys Ala Asn Val Asp Arg Val Val Arg Glu Leu Gly
 565 570 575

10 Val Asp His Arg Tyr Leu Gly Thr Pro His Met Asn Ala Ile Phe Val
 580 585 590

15 Asp Ser Leu His Arg His Ser Asn Val Cys Asn Gly Cys Phe Lys Thr
 595 600 605

Ile Tyr Thr Leu Gly Ile Asn Leu Ala His Glu Val Gly Val Ser Asp
 610 615 620

20 Ile Val Met Gly Leu Ser Lys Gly Gln Leu Phe Glu Thr Arg Leu Ser
 625 630 635 640

25 Glu Leu Phe Arg Ala Ser Thr Phe Asp Asn Gln Val Phe Glu Lys Asn
 645 650 655

30 Leu Met Glu Ala Arg Lys Ile Tyr His Arg Ile Asp Asp Ala Ala Ala
 660 665 670

35 Arg Leu Leu Asp Thr Ser Cys Val Arg Asn Asp Arg Leu Leu Glu Ser
 675 680 685

Thr Arg Phe Ile Asp Phe Tyr Arg Tyr Cys Ser Val Ser Arg Lys Asp
 690 695 700

40 Met Tyr Arg Tyr Ile Ala Glu Arg Val Gly Trp Ser Arg Pro Ala Asp

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	705		710		715		720
5	Thr Gly Arg Ser Thr Asn Cys Leu Leu Asn Asp Val Gly Ile Tyr Met	725		730		735	
10	His Lys Lys Gln Arg Gly Tyr His Asn Tyr Ser Leu Pro Tyr Ser Trp	740		745		750	
15	Asp Val Arg Val Gly His Ile Pro Arg Glu Asp Ala Met Arg Glu Leu	755		760		765	
20	Glu Asp Thr Asp Asp Ile Asp Glu Ala Lys Val Leu Gly Leu Leu Lys	770		775		780	
25	Gln Ile Gly Tyr Asp Ser Ser Leu Ile Asp Thr Gln Ala Gly Asp Ala	785		790		795	800
30	Gln Leu Ile Ala Tyr Tyr Val Ala Ala Glu Glu Leu Asp Pro Val Ala	805		810		815	
35	Leu Arg Asn Phe Ala Ala Ala Ile Leu Pro Glu Tyr Met Leu Pro Ser	820		825		830	
40	Tyr Phe Val Arg Leu Asp Arg Met Pro Leu Thr Pro Asn Gly Lys Val	835		840		845	
	Asn Arg Arg Ala Leu Pro Arg Pro Glu Leu Lys Lys Asn Ala Ser Glu	850		855		860	
	Ala His Thr Glu Pro Ser Ser Ala Leu Glu Gln Glu Leu Val Gln Ile	865		870		875	880

Trp Lys Glu Val Leu Met Val Asp Lys Val Gly Val Arg Asp Asn Phe
885 890 895

5 Phe Glu Leu Gly Gly His Ser Leu Ser Ala Leu Met Leu Leu Tyr Ser
900 905 910

10 Ile Ala Glu Arg Tyr Gln Lys Met Val Ser Ile Gln Ala Phe Ser Val
915 920 925

15 Asn Pro Thr Ile Glu Gly Leu Ser Glu His Leu Val Ala
930 935 940

<210> 30
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20 <212> PRT
<213> Xanthomonas albilineans

<400> 30

25 Met Asp Leu Gln Cys Ala Arg Ile Ala Ala Leu Cys Glu Gln Leu Lys
1 5 10 15

30 Leu Ala Arg Leu Ser Ser Asp Trp Gln Ala Leu Ala Gln Ala Ala Ala
20 25 30

Cys Glu Asp Ala Ser Tyr Phe Leu Glu Lys Val Leu Ala Ser Glu Gln
35 35 40 45

Leu Ala Arg Glu Glu Arg Lys Arg Thr Val Leu Thr Arg Leu Ala Arg
50 55 60

40 Met Pro Ser Ile Lys Thr Leu Glu Gln Phe Asp Trp Ala Gln Ala Gly

	65		70		75		80
5	Gly Ala Ser Lys Ala Gln Ile Val Glu Leu Gly His Leu Thr Phe Val						
		85		90		95	
10	Glu Arg Ala Glu Asn Val Val Met Leu Gly Pro Ser Gly Val Gly Lys						
		100		105		110	
15	Thr His Ile Ala Leu Ala Leu Cys Gln Arg Ala Val Met Ala Gly His						
		115		120		125	
20	Lys Ala Arg Phe Ile Thr Ala Ala Asp Leu Met Met Gln Leu Ala Ala						
		130		135		140	
25	Val Lys Ala Gln Asn Arg Leu Lys Asp Tyr Phe Asn Arg Ala Val Leu						
		145		150		155	160
30	Gly Pro Lys Leu Leu Val Val Asp Glu Ile Gly Tyr Leu Pro Phe Gly						
		165		170		175	
35	Arg Glu Pro Ala Gln Gly Cys Trp Ala Ala Thr Gly Phe Ala Leu Arg						
		180		185		190	
40	Ser Leu Ala Ala Arg Arg Trp Lys Thr Pro Gly Gly Ser Asp Leu Leu						
		195		200		205	
45	Arg Arg Phe Lys Gly Lys Trp Val Lys Phe Lys Ser Ala Leu Thr Ala						
		210		215		220	
50	Asp Val Val Tyr Leu Ile Phe Arg Leu Arg Gly Ser Asp His Pro						
		225		230		235	

<210> 31
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 5 <213> Xanthomonas albilineans

<400> 31

10 Met Pro Arg Ile Glu Tyr Cys Ile Ser Met Met His Arg Arg Lys Pro
 1 5 10 15

15 Thr Thr Asn Arg Ser Val Cys Met Arg Asp Ile Glu Arg Thr Ala Leu
 20 25 30

20 Trp Val Ala Gly Met Arg Ala Leu Glu Ser Glu Arg Glu Gln Ala Leu
 35 40 45

Phe His Asp Pro Phe Ala Arg Arg Leu Ala Gly Asp Glu Phe Val Glu
 50 55 60

25 Glu Leu Arg Arg Asn Asn Gln Asn Val Pro Met Pro Pro Ala Ile Glu
 65 70 75 80

30 Val Arg Thr Arg Trp Leu Asp Asp Lys Ile Met Gln Ala Val Ser Glu
 85 90 95

35 Gly Ile Gly Gln Val Val Ile Leu Ala Ala Gly Met Asp Ala Arg Ala
 100 105 110

Tyr Arg Leu Pro Trp Pro Ser Asp Thr Arg Val Tyr Glu Ile Asp His
 115 120 125

40 Met Asp Val Leu Ser Asp Lys His Glu Lys Leu His Asp Ala Gln Pro

	130	135	140
5	Val Cys Gln Arg Ile Ala Leu Pro Ile Asp Leu Arg Glu Asp Trp Pro 145	150	155 160
10	Gln Ala Leu Lys Glu Ser Gly Phe Val Gly Ser Ala Ala Thr Leu Trp 165	170	175
15	Leu Val Glu Gly Leu Leu Cys Tyr Leu Ser Ala Glu Ala Val Met Leu 180	185	190
20	Leu Phe Ala Arg Ile Asp Ala Leu Ser Ala Lys Gly Ser Ser Val Leu 195	200	205
25	Phe Asp Val Ile Gly Leu Ser Met Leu Asn Ser Pro Asn Ala Arg Val 210	215	220
30	Leu His Ala Met Ala Arg Gln Phe Gly Thr Asp Glu Pro Glu Ser Leu 225	230	235 240
35	Ile Gln Pro Leu Gly Trp Glu Pro Gly Val Leu Thr Ile Ala Ala Ala 245	250	255
40	Gly Gln Gln Met Gly Arg Trp Pro Phe Pro Val Ala Pro Arg Gly Thr 260	265	270
	His Gly Val Pro Gln Ser Tyr Leu Val His Ala Leu Lys Arg 275	280	285
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<212> PRT

<213> Xanthomonas albilineans

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Met Arg Arg Ser Pro Tyr Pro Arg Thr Leu Met Asp Ser Pro Leu Thr
1 5 10 15

10

Asn Leu Pro Met His Ser Gly Thr Glu Leu Asp Leu Arg Trp Ser Val
20 25 30

15

Gly Gln Thr Arg Pro Gly Arg Asn Glu Ala Tyr Ala Arg Gln Trp Thr
35 40 45

20

Thr Leu Leu His Gln Trp Arg Arg Asp Tyr Pro Gly Leu Arg Ile Asp
50 55 60

Val Ser Asp Thr Pro Ile Gly Gln His Ile Thr Ile Asp Tyr Ala Ala
65 70 75 80

25

Pro Tyr Pro Cys Gly Ser Phe Gly Ser Leu Leu Arg Glu Tyr Ala Arg
85 90 95

30

Leu Gly Lys Leu Ala Gly Leu Ile Cys Asp Tyr Leu Lys His Arg His
100 105 110

35

Gln Ile Val Leu Ser Glu Ser Pro Pro Gly Ala Asn Thr Leu Ala Leu
115 120 125

40

Asp Leu Gly Arg Ile Glu Glu Pro Lys Gln Leu Asp Arg Leu Gln Gly
130 135 140

	Ala Leu Gly Met Ala Leu Glu Ala Leu Ala Thr Arg Arg Ser Asp Gly	
	145	150 155 160
5	Leu Leu Leu Trp His Ala Asp His Arg Gln Arg Asn Leu Pro Asp Leu	
	165	170 175
10	Arg Asp Ser Ala Val Cys Gly Ser Ala Ala Gln Ile Ser Leu Pro Ala	
	180	185 190
15	Leu Ser Cys Val Glu Asp Leu Ile Glu Val Asp Thr Ser Leu Leu Ala	
	195	200 205
20	Cys Asp His Gly Lys Leu Cys Gln Ile Ala Ser His Leu Pro Ala Ser	
	210	215 220
25	Trp Phe Ala Arg Ser Thr Asp Gly Pro Met Pro Ser Trp Ser Asp Ala	
	225	230 235 240
30	Ser Thr Ala Val Phe Ala Cys Ala Pro Ile Gly Phe Leu Pro Ser Val	
	245	250 255
35	Gln Val Asn Val Cys Ala Gln Ile Phe Ser Ala Ala His Leu Ala Ser	
	260	265 270
40	Thr Ala Gln Met Ile Asp Pro Leu Arg Gln Gln Ala Phe Ser Tyr Arg	
	275	280 285
	Gln Leu Arg Ser Arg Ala Ala Thr Tyr Ala Arg His Leu Ser Leu Leu	
	290	295 300
	Gly Leu Gln Ser Gly Asp Ala Val Ala Leu Ile Ala Ile Asp Ser Leu	

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305

310

315

320

5

Ala Gly Val Ala Leu Met Leu Ala Cys Leu Ala Gly Gly Leu Val Phe
325 330 335

10

Ala Pro Ile Asn Glu Leu Val Ser Leu Val His Phe Glu Thr Thr Leu
340 345 350

15

Lys Thr Ile Lys Pro Arg Leu Val Leu Ile Asp Ala Glu Leu Pro Pro
355 360 365

Ser His His Ala Ala Leu Arg His Leu Pro Thr Leu Glu Leu Thr Ser
370 375 380

20

Leu Met Pro Val Ile Glu Asn Asp Glu Leu Val Val Ala Pro Cys Ser
385 390 395 400

25

Ala Asp Ala Pro Ala Val Met Ile Cys Thr Ser Gly Ser Thr Gly Thr
405 410 415

30

Pro Lys Ala Val Thr His Ser His Ala Asp Phe Met His Cys His Leu
420 425 430

35

Asn Tyr Gln Gln Ala Val Leu Gly Leu Arg Ser Asp Asp Val Met Tyr
435 440 445

Thr Pro Ser Arg Leu Phe Phe Ala Tyr Gly Leu Asn Asn Leu Met Leu
450 455 460

40

Ser Leu Leu Ala Gly Val Ser His Val Ile Ala Ala Pro Leu Ser Val
465 470 475 480

Arg Gln Ile Ala Gln Thr Ile His Thr Tyr His Val Thr Val Leu Leu
 485 490 495

5

Ala Val Pro Ala Val Phe Lys Leu Leu Leu Ala Glu Ala Ala Pro Asp
 500 505 510

10

Ala Val Trp Pro Ala Leu Arg Leu Cys Ile Ser Ala Gly Glu Ser Leu
 515 520 525

15

Pro Ala Arg Leu Gly His Ala Ile Ser Thr Arg Trp Gln Val Glu Val
 530 535 540

20

Leu Asp Gly Ile Gly Cys Thr Glu Val Leu Ser Thr Phe Ile Ser Asn
 545 550 555 560

25

Arg Pro Gly His Ala Leu Met Gly Cys Thr Gly Thr Pro Val Pro Gly
 565 570 575

30

Phe Val Val Lys Leu Val Asn Lys Gln Gly Glu Ile Cys Arg Ile Gly
 580 585 590

35

Glu Val Gly Ser Leu Trp Val Arg Gly Asn Thr Leu Thr Arg Gly Tyr
 595 600 605

40

Val Gly Asp Pro Ile Leu Ser Ala Gln Leu Phe Val Asp Gly Trp Phe
 610 615 620

Asp Thr Arg Asp Leu Phe Phe Ala Asp Ala Lys Gly Arg Phe His Asn
 625 630 635 640

	Leu	Gly	Arg	Met	Gly	Ser	Ala	Ile	Lys	Ile	Asn	Gly	Cys	Trp	Leu	Ser	
					645					650					655		
5	Pro	Glu	Thr	Leu	Glu	Ser	Val	Ile	Gln	Thr	His	Ala	Cys	Val	Lys	Glu	
				660					665					670			
10	Cys	Ala	Ile	Cys	Leu	Ile	Glu	Asp	Glu	Phe	Gly	Leu	Pro	Arg	Pro	Ala	
		675						680					685				
15	Ala	Phe	Val	Val	Pro	Val	Asp	Ala	Ser	Ile	Asp	Thr	Gly	Ala	Leu	Trp	
		690					695					700					
20	Ala	Ala	Leu	Arg	Ala	Leu	Cys	Lys	Asn	Ala	Leu	Gly	Lys	His	His	Tyr	
	705					710					715				720		
25	Pro	His	Leu	Phe	Val	Glu	Val	Ser	Thr	Ile	Pro	Arg	Thr	Cys	Ser	Gly	
					725					730					735		
30	Lys	Val	Ile	Arg	Pro	Ala	Leu	Leu	Glu	Thr	Leu	Ala	Ser	Ala	Lys	His	
				740					745					750			
35	Leu	Gln	Ser	His	Leu	Phe	Phe	Val	Gly	His	Ala	Arg	Thr				
		755						760					765				
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	<211>	330															
	<212>	PRT															
	<213>	Xanthomonas albilineans															
	<400>	33															
40	Met	His	Thr	Asn	Ala	Asp	Leu	Pro	Leu	Thr	Ile	Lys	Ala	Asp	Ser	Ala	
	1				5					10					15		

Glu Ala Thr Leu Thr Asp Trp Asn Ala Thr His Arg Ala Thr Trp Pro
 20 25 30
 5
 Thr Leu Leu Trp Gln His Arg Ala Leu Leu Phe Arg Gly Phe Ala His
 35 40 45
 10
 Pro Gly Gly Leu Glu Gln Ile Ser Arg Cys Phe Phe Asp Glu Arg Leu
 50 55 60
 15
 Ala Tyr Thr Tyr Arg Ser Thr Pro Arg Thr Asp Val Gly Gln His Val
 65 70 75 80
 20
 Tyr Thr Ala Thr Glu Tyr Pro Arg Gln Leu Ser Ile Ala Gln His Cys
 85 90 95
 25
 Glu Asn Ala Tyr Gln Arg Val Trp Pro Met Lys Leu Leu Phe His Cys
 100 105 110
 30
 Val Gln Pro Ala Ser Glu Gly Gly Cys Thr Pro Leu Ala Asp Met Leu
 115 120 125
 35
 Lys Val Thr Ala Ala Ile Asp Pro Gln Val Arg Glu Ile Phe Ala Arg
 130 135 140
 40
 Lys Gln Val Arg Tyr Val Arg Asn Tyr Arg Ala Gly Val Asp Leu Pro
 145 150 155 160
 Trp Glu Asp Val Phe Asn Thr Arg Asn Lys Gln Glu Val Glu Ala Tyr
 165 170 175

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Cys Ala Arg Asn Asp Met Gln Cys Glu Trp Thr Gly Asp Gly Leu Arg
 180 185 190

5 Thr Ser Gln Ile Cys Arg Ala Phe Ala Cys His Pro Ala Thr Gly Asp
 195 200 205

10 Glu Val Trp Phe Asn Gln Ala His Leu Phe His Tyr Thr Ala Leu Glu
 210 215 220

15 Ala Ala Ala Gln Lys Met Met Leu Ser Phe Phe Gly Glu Gln Gly Leu
 225 230 235 240

Pro Arg Asn Ala Tyr Phe Gly Asp Gly Thr Pro Ile Asp Pro Ala Met
 245 250 255

20 Leu Asp His Val Arg Thr Val Phe Ala Gln His Lys Ile His Phe Asp
 260 265 270

25 Trp His Arg Asp Asp Val Leu Leu Ile Asp Asn Met Leu Val Ser His
 275 280 285

30 Gly Arg Glu Pro Tyr Glu Gly Ser Arg Lys Ile Leu Val Cys Met Ala
 290 295 300

35 Glu Pro Tyr Ser Pro Glu Gln Ser Ser Pro Asp Ile Ala Ala Arg Ser
 305 310 315 320

Asp Gly Glu Ala Met Leu Lys Leu His Val
 325 330

40 <210> 34

<211> 1959
 <212> PRT
 <213> Xanthomonas albilineans

5 <400> 34

Met Lys Leu Ser Ser Met Ser Leu Leu Asp Ala Glu Asp Val Ala Leu
 1 5 10 15

10

Thr Ala Ala Ser Pro Asp Thr Ala Leu Ala Leu Asp Trp Ser Arg Ser
 20 25 30

15

Val Leu Asp Leu Phe Asp Ala Gln Val Ala Leu His Ala Glu Glu Leu
 35 40 45

20

Ala Cys Ala Asp Gln His Arg Gln Leu Ser Tyr Ala Gln Leu Asp Gln
 50 55 60

25

His Ala Asn Arg Leu Ala His Cys Leu Ile Glu Arg Gly Leu Arg Pro
 65 70 75 80

Gln Glu Arg Val Ala Leu Trp Phe Gly Arg Ser Pro Asp Phe Leu Ile
 85 90 95

30

Ala Leu Leu Gly Val Leu Lys Ala Gly Gly Cys Tyr Val Pro Leu Asp
 100 105 110

35

Pro His Tyr Pro Thr Thr Tyr Ile Gln Gln Ile Leu Asp Asp Ala Gln
 115 120 125

40

Pro Arg Leu Leu Leu Cys Gly Lys Asp Ile Asp Gly Gln Leu Ile Gln
 130 135 140

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	Val	Pro	Arg	Leu	Arg	Leu	Asp	Asp	Ala	Ala	Ile	Ala	Arg	Gln	Pro	His	145	150	155	160
5	Thr	Pro	Leu	Pro	His	Ala	Leu	His	Pro	Ala	Gln	Leu	Ala	Tyr	Val	Met	165	170	175	
10	Tyr	Thr	Ser	Gly	Ser	Thr	Gly	Arg	Pro	Lys	Gly	Val	Met	Val	Pro	His	180	185	190	
15	Arg	Gln	Ile	Leu	Asn	Trp	Leu	His	Ala	Leu	Trp	Ala	Arg	Ala	Pro	Phe	195	200	205	
20	Glu	Ala	Gly	Glu	Arg	Val	Ala	Gln	Lys	Thr	Ser	Ile	Ala	Phe	Ala	Ile	210	215	220	
25	Ser	Val	Lys	Glu	Leu	Leu	Ala	Gly	Leu	Leu	Ala	Gly	Val	Pro	Gln	Val	225	230	235	240
30	Phe	Ile	Asp	Glu	Asp	Thr	Val	Arg	Asp	Ile	Pro	Ala	Phe	Val	Arg	Ala	245	250	255	
35	Leu	Glu	Thr	Trp	Gln	Ile	Thr	Arg	Leu	Tyr	Thr	Phe	Pro	Ser	Gln	Leu	260	265	270	
40	Asn	Ala	Leu	Leu	Asp	His	Val	Ala	Glu	Thr	Pro	Gln	Arg	Leu	Ala	Arg	275	280	285	
	Leu	Arg	Gln	Leu	Phe	Val	Ser	Ile	Glu	Pro	Cys	Pro	Ala	Glu	Leu	Leu	290	295	300	
	Gln	Arg	Leu	Arg	Thr	Leu	Leu	Pro	Ala	Cys	Thr	Ala	Trp	Tyr	Ile	Tyr				

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	305		310		315		320
5	Gly Cys Thr Glu Ile Asn Asp Met Thr Tyr Cys Asp Pro Ala Glu Gln						
		325		330		335	
10	His Ser Gly Ser Gly Phe Val Pro Val Gly Arg Pro Ile Ala Asn Thr						
		340		345		350	
15	Lys Val His Val Leu Asp Glu Gln Leu Arg Pro Leu Pro Pro Gly Ile						
		355		360		365	
20	Met Gly Glu Val His Ile Glu Ser Leu Gly Ile Thr His Gly Tyr Trp						
		370		375		380	
25	Arg Gln Gly Gly Leu Thr Ala Ala Arg Phe Ile Ala Asn Pro Tyr Gly						
		385		390		395	400
30	Pro Pro Gly Ser Arg Leu Tyr Arg Thr Gly Asp Met Ala Arg Leu Leu						
		405		410		415	
35	Asp Asn Gly Thr Leu Glu Leu Leu Gly Arg Arg Asp Tyr Glu Val Lys						
		420		425		430	
40	Val Arg Gly Tyr Arg Val Asp Val Arg Gln Val Glu Lys Ala Leu Ala						
		435		440		445	
45	Ala His Leu Gln Val Ala Glu Ala Ala Val Ile Gly Trp Pro Gln Gly						
		450		455		460	
50	Ser Pro Thr Pro Glu Leu Leu Ala Tyr Val Val Pro Arg Gln Gly Val						
		465		470		475	480

Leu Asn Leu Asp Glu Leu Arg Lys Leu Leu Gln Glu Arg Leu Pro Thr
 485 490 495

5

Tyr Met Leu Pro Thr Arg Phe Gln Ser Leu Pro Ala Leu Pro Arg Leu
 500 505 510

10

Pro Asn Gly Lys Leu Asp Thr Leu Ser Leu Pro Glu Pro Gln Ala Ala
 515 520 525

15

Ser Ser Asp Ser Asp Tyr Leu Ala Pro Arg Ser Glu Val Glu Ile Thr
 530 535 540

20

Leu Ala Lys Leu Trp Ser Glu Leu Leu Thr Pro Ala Gln Ala Ala Pro
 545 550 555 560

Leu Arg Val Ser Leu Asn Asp Asn Phe Phe Asn Leu Gly Gly His Ser
 565 570 575

25

Leu Leu Ala Thr Gln Leu Phe Ser Arg Ile Arg Gln Ser Phe Asp Ile
 580 585 590

30

Glu Val Arg Val Asn Thr Leu Phe Glu Ser Pro Val Leu Glu Asp Phe
 595 600 605

35

Ala Arg Val Val Asn Glu Ala Arg Gln Gln Gln Ala Pro Thr Gly Gly
 610 615 620

40

Asn Thr Ile Ser Ser Arg Ala Val Arg Asp Ala Pro Val Pro Leu Ser
 625 630 635 640

	Tyr	Gln	Gln	Glu	Arg	Leu	Trp	Phe	Val	His	Glu	His	Met	Pro	Glu	Gln	
						645					650				655		
5	Arg	Thr	Ser	Tyr	Asn	Val	Ala	Phe	Ala	Cys	His	Leu	Arg	Ser	Ala	Asp	
					660				665					670			
10	Phe	Ser	Met	Ser	Ala	Leu	Arg	Glu	Ala	Ile	Gln	Ala	Leu	Val	Ala	Arg	
			675					680						685			
15	His	Glu	Thr	Leu	Arg	Thr	Arg	Ile	Ala	Thr	Cys	Ala	Gly	Gly	Asp	Tyr	
		690					695					700					
20	Pro	Ser	Gln	His	Ile	Ala	Asp	Ala	Met	Gln	Val	Pro	Val	Pro	Cys	Ile	
	705					710					715				720		
25	Thr	Ala	Thr	Pro	Ala	Glu	Val	Pro	Arg	Leu	Val	Ala	Glu	His	Ala	Ala	
					725					730					735		
30	His	Val	Phe	Asp	Leu	Ala	His	Gly	Pro	Leu	Leu	Lys	Val	Ser	Val	Leu	
				740					745					750			
35	Arg	Val	Ser	Asp	Asp	Tyr	His	Val	Phe	Leu	Met	Asn	Met	His	His	Ile	
		755						760					765				
40	Ile	Cys	Asp	Gly	Trp	Ser	Ile	Asn	Leu	Ile	Phe	His	Asp	Leu	Arg	Ala	
	770						775						780				
	Phe	Tyr	Ile	Ala	Ala	Leu	Gln	Gln	Thr	Pro	Pro	Ala	Leu	Pro	Pro	Leu	
	785					790					795				800		
	Leu	Leu	Gln	Tyr	Ala	Asp	Tyr	Ala	Thr	Trp	Gln	Arg	Val	Gln	Asp	Phe	

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805

810

815

5

Ser Ala Asp Leu Asp Tyr Trp Lys Gln Arg Leu His Gly Tyr Glu Glu
 820 825 830

10

Gly Leu Ala Leu Pro Tyr Asp Phe Pro Arg Pro Ala Asn Arg Ala Trp
 835 840 845

15

Arg Ala Gly Ile Leu His Leu Thr Tyr Pro Asp Ala Leu Ala Ala Arg
 850 855 860

Leu Ala Ala Phe Ser Gln Glu Arg Arg Val Thr Leu Phe Met Thr Leu
 865 870 875 880

20

Met Ala Ser Leu Ala Ile Val Leu His Gln Tyr Thr Gly Arg Arg Glu
 885 890 895

25

Leu Cys Leu Gly Thr Thr Ser Ala Gly Arg Asp Gln Leu Glu Thr Glu
 900 905 910

30

Asn Leu Ile Gly Phe Phe Val Asn Ile Leu Ala Val Arg Leu Asn Leu
 915 920 925

35

Gly Ser His Ala Phe Ala Glu Asp Phe Leu Gln His Val Arg Gln Gln
 930 935 940

Val Leu Asp Ala Tyr Ala His Arg Ala Leu Pro Phe Glu His Val Leu
 945 950 955 960

40

Ser Ala Leu Lys Lys Pro Arg Asp Ser Ser Gln Ile Pro Leu Val Pro
 965 970 975

Ile Met Leu Arg His Gln Asn Phe Ala Thr Glu Gly Val Asn Ala Phe
 980 985 990

5

Ala Gln Ile Phe Leu Ser Ala Gln Met Glu Phe Gly Glu Arg Thr Thr
 995 1000 1005

10

Pro Asn Glu Leu Asp Leu Gln Phe Ile Gly Asp Gly Ser His Leu
 1010 1015 1020

15

Glu Val Thr Val Glu Tyr Ala Ala Glu Leu Phe Ser Ala Ala Thr
 1025 1030 1035

20

Val Gln Arg Met Leu Ala His His Gln Arg Val Leu Glu Arg Met
 1040 1045 1050

25

Leu Glu Glu Pro Arg Cys Arg Leu Ser Asp Phe Ser Leu Pro Val
 1055 1060 1065

30

Ala Arg Thr Glu Phe Thr Pro His Thr Leu Asp Thr Ser Arg Ser
 1070 1075 1080

35

Val Leu Asp Leu Phe Asp Ala Gln Val Ala Leu His Ala Glu Glu
 1085 1090 1095

40

Leu Ala Cys Ala Asp Gln His Arg Gln Leu Ser Tyr Ala Gln Leu
 1100 1105 1110

Asp Gln His Ala Asn Arg Leu Ala His Cys Leu Ile Glu Arg Gly
 1115 1120 1125

	Leu Arg	Pro Gln Glu Arg Val	Ala Leu Trp Phe Gly	Arg Ser Pro
	1130	1135	1140	
5	Asp Phe	Leu Ile Ala Leu Leu	Gly Val Leu Lys Ala	Gly Gly Cys
	1145	1150	1155	
10	Tyr Val	Pro Leu Asp Pro His	Tyr Pro Thr Thr Tyr	Ile Gln Gln
	1160	1165	1170	
15	Ile Leu	Asp Asp Ala Gln Pro	Arg Leu Leu Leu Cys	Gly Lys Asp
	1175	1180	1185	
20	Ile Asp	Gly Gln Leu Ile Gln	Val Pro Arg Leu Arg	Leu Asp Asp
	1190	1195	1200	
25	Ala Ala	Ile Ala Arg Gln Pro	His Thr Pro Leu Pro	His Ala Leu
	1205	1210	1215	
30	His Pro	Ala Gln Leu Ala Tyr	Val Met Tyr Thr Ser	Gly Ser Thr
	1220	1225	1230	
35	Gly Arg	Pro Lys Gly Val Met	Val Pro His Arg Gln	Ile Leu Asn
	1235	1240	1245	
40	Trp Leu	His Ala Leu Trp Ala	Arg Ala Pro Phe Glu	Ala Gly Lys
	1250	1255	1260	
	Arg Val	Ala Gln Lys Thr Ser	Ile Ala Phe Ala Ile	Ser Val Lys
	1265	1270	1275	
	Glu Leu	Leu Ala Gly Leu Leu	Ala Gly Val Pro Gln	Val Phe Ile

	1280	1285	1290
5	Asp Glu 1295	Asp Thr Val Arg Asp 1300	Ile Pro Ala Phe Val Arg Ala Leu 1305
10	Glu Thr 1310	Trp Gln Ile Thr Arg 1315	Leu Tyr Thr Phe Pro Ser Gln Leu 1320
15	Asn Ala 1325	Leu Leu Asp His Val 1330	Ala Glu Thr Pro Gln Arg Leu Ala 1335
20	Arg Leu 1340	Arg Gln Leu Phe Val 1345	Ser Ile Glu Pro Cys Pro Ala Glu 1350
25	Leu Leu 1355	Gln Arg Leu Arg Thr 1360	Leu Leu Pro Ala Cys Thr Ala Trp 1365
30	Tyr Ile 1370	Tyr Gly Cys Thr Glu 1375	Ile Asn Asp Met Thr Tyr Cys Asp 1380
35	Pro Ala 1385	Glu Gln His Ser Gly 1390	Ser Gly Phe Val Pro Val Gly Arg 1395
40	Pro Ile 1400	Ala Asn Thr Lys Val 1405	His Val Leu Asp Glu Gln Leu Arg 1410
	Pro Leu 1415	Pro Pro Gly Ile Met 1420	Gly Glu Val His Ile Glu Ser Leu 1425
	Gly Ile 1430	Thr His Gly Tyr Trp 1435	Arg Gln Gly Gly Leu Thr Ala Ala 1440

	Arg Phe	Ile Ala Asn Pro Tyr	Gly Pro Pro Gly Ser	Arg Leu Tyr
	1445	1450	1455	
5	Arg Thr	Gly Asp Met Ala Arg	Leu Leu Asp Asn Gly	Thr Leu Glu
	1460	1465	1470	
10	Leu Leu	Gly Arg Arg Asp Tyr	Glu Val Lys Val Arg	Gly Tyr Arg
	1475	1480	1485	
15	Val Asp	Val Arg Gln Val Glu	Lys Ala Leu Ala Ala	His Leu Gln
	1490	1495	1500	
20	Val Ala	Glu Ala Ala Val Ile	Gly Trp Pro Gln Gly	Ser Pro Thr
	1505	1510	1515	
25	Pro Glu	Leu Leu Ala Tyr Val	Val Pro Arg Gln Gly	Val Leu Asn
	1520	1525	1530	
30	Leu Asp	Glu Leu Arg Lys Leu	Leu Gln Glu Arg Leu	Pro Thr Tyr
	1535	1540	1545	
35	Met Leu	Pro Thr Arg Phe Gln	Ser Leu Pro Ala Leu	Pro Arg Leu
	1550	1555	1560	
40	Pro Asn	Gly Lys Leu Asp Thr	Leu Ser Leu Pro Glu	Pro Gln Ala
	1565	1570	1575	
	Ala Ser	Ser Asp Ser Asp Tyr	Leu Ala Pro Arg Ser	Glu Val Glu
	1580	1585	1590	

	Ile Thr	Leu Ala Lys Leu Trp	Ser Glu Leu Leu Thr	Pro Ala Gln
	1595	1600	1605	
5	Ala Ala	Pro Leu Arg Val Ser	Leu Asn Asp Asn Phe	Phe Asn Leu
	1610	1615	1620	
10	Gly Gly	His Ser Leu Leu Ala	Thr Gln Leu Phe Ser	Arg Ile Arg
	1625	1630	1635	
15	Gln Ser	Phe Asp Ile Glu Val	Arg Val Asn Thr Leu	Phe Glu Ser
	1640	1645	1650	
20	Pro Val	Leu Glu Asp Phe Ala	Ala Val Val Glu Arg	Gly Met Arg
	1655	1660	1665	
25	Gln Ser	Gln Ala Gly Ser Met	Pro Val Ser Leu Ile	Val Pro Leu
	1670	1675	1680	
30	Ser Leu	Arg Thr Glu Arg Ala	Ala Val Tyr Ala Ile	His Pro Ile
	1685	1690	1695	
35	Gly Gly	Gln Ile His Cys Tyr	Ile Asp Leu Ala Ala	Ala Leu Gly
	1700	1705	1710	
40	His Ser	Ala Arg Val Tyr Gly	Leu Gln Cys Glu Pro	Val Arg Arg
	1715	1720	1725	
	Phe Ala	His Leu Ser Asp Leu	Ala Ala His Tyr Cys	Asp Ala Leu
	1730	1735	1740	
	Leu Ala	Gly Pro Thr Gly Ala	Pro Tyr Arg Leu Leu	Gly Trp Ser

	1745		1750		1755
5	Ser Gly 1760	Gly Val Leu Ala Leu	Ala Val Ala Glu Gln	Leu Gln Arg	
			1765	1770	
10	Arg Gly 1775	Leu Arg Val Asp Tyr	Val Gly Leu Leu Asp	Ser Ser Leu	
			1780	1785	
15	Ile Pro 1790	Val His Ala Arg Glu	Pro Arg Gln Leu Thr	Phe Val Ala	
			1795	1800	
	Ala Leu 1805	Asn Thr Leu Ala Ala	Leu Ala Lys Arg Gly	Phe Glu Gln	
			1810	1815	
20	Ala Glu 1820	Ile Asp Glu Ala Arg	Gln Leu Leu Phe Ala	Asp Gly Asp	
			1825	1830	
25	Asp Glu 1835	His Val Phe Asp Tyr	Ser Arg His Gln Ala	Ser Leu Asp	
			1840	1845	
30	Lys Leu 1850	Leu Ala His Leu Arg	Phe Thr Leu Glu Ser	Arg Met Trp	
			1855	1860	
	Pro Pro 1865	Leu Ala Glu Gln Leu	Arg Val Thr Arg Tyr	His Leu Gly	
			1870	1875	
35	Leu Leu 1880	Ala Gly Phe Glu Pro	Gln Cys Leu Gln Pro	Asn Ala His	
			1885	1890	
40	Leu Tyr 1895	Gln Ala Gln Thr Ala	Val His Val Ser Tyr	Ala Asp Met	
			1900	1905	

Ser Lys Pro Arg Gly Gly Ser Glu Val Leu Pro Asp Ile Thr Gly
 1910 1915 1920

5

Tyr Val Pro Leu Ser Gln Ile Lys Ser Ala Ala Gly Asn His Tyr
 1925 1930 1935

10

Ser Met Leu Gln Gly Asp Pro Leu Arg Glu Leu Ala Arg Met Leu
 1940 1945 1950

15

Val Thr Asp Leu Asp Ala
 1955

<210> 35
 <211> 83
 <212> PRT
 <213> Xanthomonas albilineans

<400> 35

25

Met Thr Phe Glu Glu Gln Ala Tyr Leu Val Leu Ile Asn Asp Glu Leu
 1 5 10 15

30

Gln Tyr Ser Leu Trp Pro Ser Asp Leu Glu Val Pro Pro Gly Trp Arg
 20 25 30

35

Lys Glu Gly Tyr Ala Gly Gly Lys Asp Glu Cys Met Ala Tyr Ile Asp
 35 40 45

40

Glu Thr Trp Thr Asp Met Arg Pro Leu Ser Leu Arg Glu Leu Asp Asp
 50 55 60

Lys Asn Leu Gly Asp Ala Ser Ser Pro Asp Gly Ser Gly Phe Glu Ser

65 70 75 80

5 Ser Tyr Ser

10 <210> 36
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<212> PRT
<213> Xanthomonas albilineans

<400> 36

15 Met Gly Cys Ala Cys Leu Pro His Tyr Leu Glu Lys Gln Asp Leu Ser
1 5 10 15

20 Ala Leu Asp Asp Ala Leu Ala Gly Val Arg Leu Ser Gln Tyr Cys Thr
20 25 30

25 Thr Asp Gly Arg Gln Leu Glu Leu Tyr Trp Leu Gly Ala Gln Ala Ser
35 40 45

30 Pro Lys Leu Val Leu Leu Pro Pro Tyr Gly Met Ser Tyr Leu Leu Leu
50 55 60

35 Ser Arg Leu Ala Gln Arg Leu Ala Arg His Phe His Val Leu Cys Trp
65 70 75 80

40 Glu Ser Ile Gly Cys Pro Asn Ala Gln Thr Ser Val Thr Ala Glu Asp
85 90 95

45 Phe Asp Leu Asp Arg Gln Ala Ala Thr Leu Leu Gly Ile Leu His Gln
100 105 110

His Asp Tyr Ala Asp Cys His Phe Val Gly Trp Cys Gln Ala Ala Gln
115 120 125

5 Leu Ala Val His Ala Ile Ala Leu His Gly Phe Ala Pro Arg Ser Met
130 135 140

10 Ala Trp Val Ala Pro Ala Gly Leu Leu Pro Pro Ile Val Lys Ser Glu
145 150 155 160

15 Phe Glu Arg Cys Ala Leu Pro Ile Tyr Leu Gln Ile Glu Arg His Gly
165 170 175

20 Leu Glu Gln Ala Lys Lys Leu Ala Ala Ile Leu Asp Lys Tyr Arg Gly
180 185 190

Gln Pro Leu Arg Gly Asp Asp Leu Ala Glu Lys Leu Thr Met Leu His
195 200 205

25 Leu Ala Asp Pro Ala Ser Thr Leu Val Phe Ser Arg Tyr Met Arg Ala
210 215 220

30 Tyr Glu Glu Asn Lys Gln Ser Val Gln Ala Leu Leu Pro Thr Ala Leu
225 230 235 240

35 Gly Arg His Pro Thr Leu Ile Val His Cys Lys Asp Asp Ser Phe Ser
245 250 255

His Tyr Ser Ala Ser Val Gln Leu Ala Arg His Asp Pro Ser Leu Arg
260 265 270

40 Leu Asp Leu Leu Asp His Gly Gly His Leu Gln Leu Phe Asn Asp Pro

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275

280

285

5

Gly Ala Val Ala Gln Arg Ile Ile Asp Phe Ile Gly Leu Thr Val Gly
 290 295 300

10

Glu Val Ala Pro Thr Ser Met His Ser Ala Ala
 305 310 315

15

<210> 37
 <211> 451
 <212> PRT
 <213> Xanthomonas albilineans

<400> 37

20

Met Tyr Ile Pro Asn Asn Ile Asp Leu Asp Pro His Ser Ala Leu Val
 1 5 10 15

25

Arg Gln Leu Thr Ser Tyr Gln Val Arg Phe Leu Gln Trp Trp Arg Leu
 20 25 30

30

Arg Gly Pro Ser Glu Phe His Asp Arg Glu Met Asn Leu Arg Met Pro
 35 40 45

35

Thr Gly Gly Val Lys Gly Ser Glu Trp Thr Arg Tyr His Arg Met Arg
 50 55 60

40

Pro Ser Asp Tyr Arg Trp Gly Val Phe Met Met Pro Pro Asp Arg Asn
 65 70 75 80

Thr Val Val Phe Gly Glu Arg Lys Gly Gln Val Ala Trp Ser Cys Val
 85 90 95

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	Pro Glu Glu Tyr Arg Asp Leu Leu Leu Asp His Val Thr Val Gln Gly
	100 105 110
5	Asp Val Glu Asn Ala Ala Val Glu Gln Ser His Glu Leu Thr Gln Met
	115 120 125
10	Val Pro Ser Ala Ile Asp Leu Glu His Leu Phe Gln Phe Phe Leu Glu
	130 135 140
15	Glu Gly Arg His Thr Trp Ala Met Ser His Leu Leu Ile Glu Tyr Phe
	145 150 155 160
20	Gly Ser Asp Gly Ala Asp Ala Ala Glu Gly Leu Leu Gln Arg Met Ser
	165 170 175
25	Glu Asp Trp Leu Ser His Phe Met Trp Cys Phe Phe Ala Asp Arg Val
	195 200 205
30	Gly Lys Tyr Gln Ile Gln Ala Val Thr Gln Ser Ala Phe Leu Pro Leu
	210 215 220
35	Ala Arg Thr Ala Arg Phe Met Met Phe Glu Glu Pro Leu His Ile Lys
	225 230 235 240
40	Phe Gly Val Asp Gly Leu Glu Arg Val Leu Tyr Arg Ser Ala Glu Ile
	245 250 255
	Thr Leu Arg Glu Asp Thr His Ala Ile Phe Asp Ala Gly Ala Ile Pro

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	260	265	270
5	Leu Pro Val Val Gln Lys Tyr 275	Leu Asn Tyr Trp 280	Leu Pro Lys Ile Phe 285
10	Asp Leu Phe Gly His Asp Val 290	Ser Glu Arg Ser Arg Val 295 300	Leu Tyr Gln
15	Ala Gly Ile Arg Ser Pro Arg Asn Phe 305 310	Asp Lys Leu Glu Gly Thr Glu 315 320	
20	Val Ala Val Asp Val Arg Cys Glu Asp 325	Arg Leu Val Ser Ser Thr Ala 330 335	
25	Pro Ala Glu Leu Ala Ile Asn Ala Val Met Arg Arg 340 345	Gln Tyr Ile Ala 350	
30	Glu Val Gly Ala Ile Ile Gly Arg Trp Asn Gln Gln Leu Arg Arg Leu 355 360 365		
35	Gly Leu Ala Phe Glu Leu Gln Leu Pro His Glu Arg Phe His Arg Asp 370 375 380		
40	Phe Gly Pro Cys Lys Gly Leu Ala Phe Asp Leu Asp Gly Asn Pro Val 385 390 395 400		
	His Asp Ala Asp Gly Gln Arg Leu Ala Ala Leu Leu Pro Thr Pro Gln 405 410 415		
	Asp Leu Ala Gly Val Arg Gly Leu Met Gly Arg Glu Leu Gly Glu Gly 420 425 430		

Arg Thr Ala Val Trp Leu Ala Pro Ala Gly Ala Ser Leu Asp Lys Leu
435 440 445

5
Met Pro Ala
450

10
<210> 38
<211> 317
<212> PRT
<213> Xanthomonas albilineans

15
<400> 38

Met Asn Ser Tyr Val Gly Cys Gln Lys Leu Glu Thr Asp Gly Asp Ala
1 5 10 15

20
Ser Arg Val Val Pro Met Trp Val Met Tyr Pro Thr Ala Thr Pro Ser
20 25 30

25
Arg Asp Thr Ala Met Gly Pro Tyr Thr Leu Asp Val Ala Leu Gly Ala
35 40 45

30
Pro Ile Glu Ala Gly Pro Phe Pro Leu Ala Val Ile Ser His Gly Thr
50 55 60

35
Arg Ser Ala Gly Leu Val Phe Arg Thr Leu Ala His Tyr Leu Ala Arg
65 70 75 80

His Gly Phe Ile Val Ala Leu Pro Glu His Pro Gly Asp Asn Leu Phe
85 90 95

40
Gln His Gln Leu Glu Tyr Ser Tyr Gln Asn Leu Glu Asp Arg Pro Arg

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	100	105	110
5	His Ile Arg Ala Val Ile Asp Thr Leu Thr Gly His Ala Gln Phe Gly 115	120	125
10	Pro Ala Ile Gln Ala His Asn Val Ala Val Ile Gly His Ser Val Gly 130	135	140
15	Gly Tyr Thr Ala Leu Ala Ile Ala Gly Gly Glu Pro His Thr Gly Phe 145	150	155 160
20	Met Val Asp Phe Ala His Arg Pro Glu His Ala Glu Gln Pro Ala Trp 165	170	175
25	Thr Ala Leu Val Arg Gln Asn Arg Val Pro Ile Arg Ala Val Pro Val 180	185	190
30	Thr Ala Asp Pro Arg Val Arg Ala Val Val Ala Leu Ala Pro Asp Phe 195	200	205
35	Ser Leu Tyr Met His Glu Asp Ala Leu Ala Lys Val Glu Val Pro Val 210	215	220
40	Leu Leu Ile Val Gly Glu Lys Asp Gln Trp Ala His Glu Thr Ile Val 225	230	235 240
	Ala Thr Arg Thr Ala Leu Gly Asn Asp Gly Arg Leu Glu Ala Arg Val 245	250	255
	Val Pro Asn Ala Gly His Tyr Ala Phe Ile Ser Val Phe Pro Glu Ala 260	265	270

Met Lys Ala Arg Val Gly Glu Ala Ala Ile Asp Pro Pro Gly Phe Asp
 275 280 285

5

Arg Ser Ala Phe Gln Arg Glu Leu Glu Arg Asp Ile Leu His Phe Leu
 290 295 300

10

Thr Val Thr Met Arg Pro Ala Glu Ala Ala Ile Ser Gly
 305 310 315

15

<210> 39
 <211> 496
 <212> PRT
 <213> Xanthomonas albilineans

20

<400> 39

Met Gln Lys Pro Lys Glu Ala Leu Gly Met Pro Pro Gly Met Ala Pro
 1 5 10 15

25

Pro Gly Ala Gln Phe Asp Tyr Arg Trp Arg Trp Pro Ala Met Ile Val
 20 25 30

30

Leu Leu Ser Ala Asn Phe Met Asn Leu Leu Asp Val Gly Ile Val Asn
 35 40 45

35

Val Ala Leu Pro Ser Ile Gln Lys Asn Leu Gly Ala Asp Glu Gln Gln
 50 55 60

40

Leu Glu Trp Ile Val Ala Ile Tyr Ile Leu Leu Phe Ala Leu Gly Leu
 65 70 75 80

Leu Pro Leu Gly Arg Leu Gly Asp Met Leu Gly Arg Lys Arg Met Phe

250

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85

90

95

5

Gly Thr Gly Val Ala Gly Phe Ile Leu Met Ser Ala Phe Cys Ala Ile
 100 105 110

10

Ala Gly Asn Ile His Val Leu Ile Ile Ala Arg Ala Leu Gln Gly Leu
 115 120 125

15

Ala Ala Ala Met Leu Ala Pro Gln Val Met Ala Ile Ala Gln Thr Met
 130 135 140

Phe Ala Pro Lys Glu Arg Ala Ala Ala Phe Ser Leu Phe Gly Leu Val
 145 150 155 160

20

Ala Gly Leu Ala Ser Phe Ala Gly Pro Leu Val Ser Gly Leu Leu Ile
 165 170 175

25

His Ile Asp Ala Phe Gly Val Gly Trp Arg Ala Ile Phe Leu Ile Asn
 180 185 190

30

Val Pro Ile Gly Leu Val Thr Leu Leu Ala Ala Ala Ile Trp Val Pro
 195 200 205

35

Lys Val Pro Ala His Ala Gly Ile His Asn Asp Trp Val Gly Ile Ala
 210 215 220

Leu Ala Ala Leu Ala Leu Leu Cys Leu Val Phe Pro Leu Ile Glu Gly
 225 230 235 240

40

Arg Ala Tyr Gly Trp Pro Leu Trp Cys Phe Ala Ala Ile Ala Leu Gly
 245 250 255

Ile Pro Leu Leu Val Ala Phe Val Ala Trp Gln Arg Arg Gln Ala His
260 265 270

5
Leu Ala Arg Pro Ala Leu Leu Pro Ile Tyr Leu Met Ser His Arg Asp
275 280 285

10
Tyr Ile Leu Gly Ala Leu Ser Val Ser Val Phe Tyr Ser Ala Leu Gln
290 295 300

15
Gly Phe Phe Leu Val Phe Val Ile Phe Leu Gln Gln Gly Leu Ala Tyr
305 310 315 320

20
Ser Ala Leu Glu Thr Gly Val Ala Thr Thr Pro Phe Pro Val Gly Val
325 330 335

25
Ala Ile Ala Ser Met Leu Ala Arg His Val Glu Ser Leu Arg Ala Lys
340 345 350

30
Ile Phe Ser Gly Ala Cys Leu Met Ile Ala Ser Tyr Leu Ala Leu Trp
355 360 365

35
Val Ile Ile Thr Arg Ser Glu Gly Ser Leu Asp Pro Trp Thr Leu Thr
370 375 380

40
Leu Pro Leu Leu Ile Gly Gly Leu Gly Cys Gly Ile Thr Ile Ala Ser
385 390 395 400

45
Leu Phe Gln Thr Val Met Arg Thr Val Pro Leu Lys Asp Ala Gly Ala
405 410 415

Gly Ser Gly Ala Leu Gln Val Ile Gln Gln Val Gly Gly Met Leu Gly
420 425 430

5 Ile Ala Leu Val Ser Glu Ile Phe Phe Ser Gly Leu His Gln His Leu
435 440 445

10 Gln Gly Pro Ala Gly Val Ala Leu Ala Phe Lys Gln Ala Phe Gly Ala
450 455 460

15 Thr Val Val Tyr Tyr Ile Ala Ala Asn Ala Phe Val Ala Leu Ser Thr
465 470 475 480

20 Leu Gly Leu Gln Phe Lys Leu Thr Gln Phe Ala Pro Gln Ser Ser Pro
485 490 495

<210> 40
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<212> PRT
<213> Xanthomonas albilineans

25 <400> 40

30 Met Lys Arg Thr Tyr Ile Gly Leu Ala Asn Ser Phe His Asp Ser Ala
1 5 10 15

Ile Ala Ile Val Gly Asp Asp Gly Gln Val Arg Phe Ala Glu Ala Thr
20 25 30

35 Glu Arg Tyr Leu Gln Tyr Lys Arg Ser Ile Gly Val Ala Pro Asp Val
35 40 45

40 Phe Gln Arg Ala Ile Lys Leu Val His Glu Tyr Gly Asp Pro Gly Ala
50 55 60

	Glu	Leu	Val	Val	Ala	Thr	Ser	Trp	Ser	Gly	Gln	Thr	Pro	Glu	Leu	Met	
	65						70				75					80	
5																	
	Arg	Glu	Gly	Leu	Gly	Lys	Thr	Ala	Gln	Ala	Val	Asp	Gln	Tyr	Arg	Ser	
				85						90					95		
10																	
	Ala	Phe	Gly	Asp	Leu	Pro	Trp	His	Val	Asn	Lys	Gln	Phe	Val	Ala	Gln	
				100					105						110		
15																	
	Ser	Phe	Phe	Tyr	Arg	Ser	Gln	Leu	Ala	Met	Val	Glu	His	Pro	Gly	His	
			115					120					125				
20																	
	Leu	Leu	Glu	Tyr	Asp	Leu	Ser	His	Met	Ala	Glu	Pro	Ala	Phe	Lys	Pro	
		130					135					140					
25																	
	Pro	Ser	Tyr	Arg	His	Tyr	Glu	His	His	Leu	Thr	His	Ala	Val	Ala	Gly	
	145					150					155					160	
30																	
	Cys	Tyr	Thr	Ser	Pro	Phe	Glu	Glu	Ala	Val	Cys	Ala	Val	Leu	Asp	Gly	
					165					170					175		
35																	
	Met	Gly	Glu	Lys	Asn	Ala	Leu	Ala	Cys	Tyr	His	Tyr	Gln	Gln	Gly	Lys	
				180					185					190			
40																	
	Leu	Thr	Pro	Ile	His	Gln	Ser	Glu	Thr	Ser	Ser	Trp	Ala	Ser	Leu	Gly	
		195						200					205				
45																	
	Phe	Phe	Tyr	Gly	Met	Ile	Cys	Glu	Val	Cys	Gly	Phe	Gly	Thr	Leu	Ser	
	210						215				220						

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Gly Glu Glu Trp Lys Val Met Gly Leu Ala Ala Tyr Gly Gln His Asp
 225 230 235 240

5 Arg Gln Leu Tyr Glu Leu Leu Arg Gln Met Leu Arg Val Asp Gly Leu
 245 250 255

10 Thr Leu Arg Phe Ala Pro Ala Ala Gln Phe Ser Gln Leu Gln Arg Thr
 260 265 270

15 Leu Tyr Ala Met Arg Arg Cys Lys Gly Gln Pro Thr Ile Glu Leu Ala
 275 280 285

20 Asn Leu Ala Tyr Ala Gly Gln Gln Val Phe Cys Asp Val Leu Phe Glu
 290 295 300

Phe Leu His Asn Leu His Ala Leu Gly Leu Ser Asp His Leu Val Leu
 305 310 315 320

25 Gly Gly Gly Cys Ala Leu Asn Ser Ser Ala Asn Gly Arg Val Leu Ala
 325 330 335

30 Glu Thr Pro Phe Arg His Leu His Val Phe Ala Ala Pro Gly Asp Asp
 340 345 350

35 Gly Asn Ala Val Gly Ala Ala Leu Trp Ala His Ala Glu Asp His Pro
 355 360 365

Glu Gln Thr Pro Pro Ala Ala Arg Glu Gln Ser Pro Tyr Leu Gly Ser
 370 375 380

40 Ser Met Ser Ala Glu Thr Leu His Asn Val Glu Arg Phe Gly Ala Leu

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	385		390		395		400									
5	Ser	Lys	Phe	Thr	Arg	Cys	Leu	Asp	Asp	Ala	Ala	Gln	Arg	Ala	Ala	Arg
					405					410					415	
10	Leu	Leu	Thr	Glu	Gly	Lys	Ile	Val	Ala	Trp	Val	Gln	Gly	Arg	Ala	Glu
				420					425					430		
15	Phe	Gly	Pro	Arg	Ala	Leu	Gly	Asn	Arg	Ser	Ile	Leu	Ala	Asp	Pro	Arg
		435						440						445		
20	Ser	Pro	Ala	Ile	Lys	Asp	Ile	Ile	Asn	Ala	Arg	Val	Lys	Phe	Arg	Glu
		450					455						460			
25	Glu	Phe	Arg	Pro	Phe	Ala	Pro	Ser	Ile	Leu	His	Glu	His	Gly	Ala	Glu
	465					470				475				480		
30	Tyr	Phe	Glu	Leu	Tyr	Gln	Glu	Ser	Pro	Tyr	Met	Glu	Arg	Thr	Leu	Lys
				485						490				495		
35	Phe	Arg	Ala	Glu	Ala	Thr	Arg	Lys	Val	Pro	Gly	Val	Val	His	His	Asp
			500						505					510		
40	Gly	Thr	Gly	Arg	Leu	Gln	Thr	Val	Lys	Gln	His	Trp	Asn	Pro	Arg	Tyr
		515					520						525			
45	His	Ala	Leu	Ile	Lys	Glu	Phe	Tyr	Arg	Leu	Thr	Gly	Ile	Pro	Leu	Val
		530					535					540				
50	Leu	Asn	Thr	Ser	Phe	Asn	Val	Met	Gly	Lys	Pro	Ile	Ala	His	Ser	Val
	545					550					555				560	

Glu Asp Ala Leu Ser Ile Phe Phe Thr Ser Gly Leu Asp Ala Met Phe
 565 570 575

5

Ile Asp Asp Val Leu Ile Glu Lys
 580

10

<210> 41
 <211> 88
 <212> PRT
 <213> Xanthomonas albilineans

15

<400> 41

Met Arg Thr Ser Lys Phe Asn Glu Thr Gln Ile Ile Ala Thr Leu Lys
 1 5 10 15

20

Gln Ala Asp Ala Gly Val Pro Val Lys Asp Ile Cys Arg Gln Val Gly
 20 25 30

25

Ile Ser Thr Ala Thr Tyr Tyr Gln Trp Lys Ser Lys Tyr Val Ala Ser
 35 40 45

30

Glu Met Pro Ser Ser Arg His Thr Ser Leu Thr Trp Arg Pro Pro Ser
 50 55 60

35

Thr Cys Phe Ser Val Ala Thr Ile Trp Leu Ser Val Asn Leu Leu Leu
 65 70 75 80

40

Arg Ile Val Gly Arg Leu Gly Gly
 85

<210> 42

<211> 716
 <212> PRT
 <213> Xanthomonas albilineans

5 <400> 42

Met Arg Cys Leu Ile Ile Asn Asn Tyr Asp Ser Phe Thr Trp Asn Leu
 1 5 10 15

10

Ala Asp Tyr Val Ala Gln Ile Phe Gly Glu Asp Pro Leu Val Val His
 20 25 30

15

Asn Asp Glu Tyr Ser Trp His Glu Leu Lys Asp Arg Gly Gly Phe Ser
 35 40 45

20

Ser Ile Ile Val Ser Pro Gly Pro Gly Ser Val Val Asn Glu Ala Asp
 50 55 60

25

Phe His Ile Ser Leu Gln Ala Leu Glu Gln Asn Glu Phe Pro Val Leu
 65 70 75 80

Gly Val Cys Leu Gly Phe Gln Gly Leu Ala His Val Tyr Gly Gly Arg
 85 90 95

30

Ile Leu His Ala Pro Val Pro Phe His Gly Arg Arg Ser Thr Val Ile
 100 105 110

35

Asn Thr Gly Asp Gly Leu Phe Glu Gly Ile Pro Gln Arg Phe Glu Ala
 115 120 125

40

Val Arg Tyr His Ser Leu Met Val Cys Gln Gln Ser Leu Pro Pro Val
 130 135 140

Leu Lys Val Thr Ala Arg Thr Asp Cys Gly Val Val Met Gly Leu Gln
 145 150 155 160

5 His Val Gln His Pro Lys Trp Gly Val Gln Phe His Pro Glu Ser Ile
 165 170 175

10 Leu Thr Glu His Gly Lys Arg Ile Val Ala Asn Phe Ala Lys Leu Ala
 180 185 190

15 Ala Arg His Ser Ala Pro Leu Leu Ala Gly Ser Glu Gln Ala Gly Lys
 195 200 205

20 Val Leu Ser Val Cys Ala Pro Glu Met Val Thr Pro Arg Val Arg Arg
 210 215 220

Met Leu Ser Arg Lys Ile Lys Cys Arg Trp Gln Ala Glu Asp Val Phe
 225 230 235 240

25 Leu Ala Leu Phe Ala Asp Glu Lys His Cys Phe Trp Leu Asp Ser Gln
 245 250 255

30 Leu Val Cys Ser Pro Met Ala Arg Tyr Ser Phe Met Gly Ala Val Asn
 260 265 270

35 Glu Ser Glu Val Val Arg His Cys Val Arg Pro Gly Ser Met Val Gln
 275 280 285

Glu Ala Gly Glu Arg Phe Leu Ala Glu Met Asp Arg Ala Leu Gln Ser
 290 295 300

40 Val Leu Thr Glu Asp Val Ala Glu Arg Pro Pro Phe Ala Phe Arg Gly

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	305		310		315		320
5	Gly Tyr Val	Gly Tyr Met	Ser Tyr Glu	Met Lys Ser	Val Phe Gly	Ala	
		325		330		335	
10	Pro Ala Ser	His Ala Asn	Ala Ile Pro	Asp Ala Leu	Trp Met Arg	Val	
		340		345		350	
15	Glu Arg Phe	Val Ala Phe	Asp His Ala	Thr Glu Glu	Val Trp Leu	Leu	
		355		360		365	
20	Ala Leu Ala	Asp Thr Glu	Asp Leu Ser	Ala Leu Ala	Trp Leu Asp	Ala	
		370		375		380	
25	Ile Glu Gln	Arg Ile His	Ala Ile Gly	Gln Ala Ala	Pro Ala Cys	Ile	
		385		390		395	400
30	Ser Leu Gly	Leu Arg Ser	Met Glu Ile	Glu Leu Asn	His Gly Arg	Arg	
		405		410		415	
35	Gly Tyr Leu	Glu Ala Ile	Glu Arg Cys	Lys Gln Arg	Ile Val Asp	Gly	
		420		425		430	
40	Glu Ser Tyr	Glu Ile Cys	Leu Thr Asp	Leu Phe Ser	Phe Gln Ala	Glu	
		435		440		445	
45	Leu Asp Pro	Leu Met Leu	Tyr Arg Tyr	Met Arg Arg	Gly Asn Pro	Ala	
		450		455		460	
50	Pro Phe Gly	Ala Tyr Leu	Arg Asn Gly	Ser Asp Cys	Ile Leu Ser	Thr	
		465		470		475	480

Ser Pro Glu Arg Phe Leu Glu Val Asp Gly His Gly Thr Ile Gln Thr
 485 490 495

5

Lys Pro Ile Lys Gly Thr Cys Arg Arg Ala Glu Asp Pro Gln Leu Asp
 500 505 510

10

Arg Asn Leu Ala Met Arg Leu Ala Ala Ser Glu Lys Asp Arg Ala Glu
 515 520 525

15

Asn Leu Met Ile Val Asp Leu Met Arg Asn Asp Leu Ser Arg Val Ala
 530 535 540

20

Val Pro Gly Ser Val Thr Val Pro Lys Leu Met Asp Ile Glu Ser Tyr
 545 550 555 560

Lys Thr Val His Gln Met Val Ser Thr Val Glu Ala Arg Leu Arg Ala
 565 570 575

25

Asp Cys Ser Leu Val Asp Leu Leu Lys Ala Val Phe Pro Gly Gly Ser
 580 585 590

30

Ile Thr Gly Ala Pro Lys Leu Arg Ser Met Glu Ile Ile Asp Gly Leu
 595 600 605

35

Glu Asn Ala Pro Arg Gly Val Tyr Cys Gly Ser Ile Gly Tyr Leu Gly
 610 615 620

40

Tyr Asn Cys Val Ala Asp Leu Asn Ile Ala Ile Arg Ser Leu Ser Tyr
 625 630 635 640

Asp Gly Gln Glu Ile Arg Phe Gly Ala Gly Gly Ala Ile Thr Phe Leu
645 650 655

5 Ser Asp Pro Gln Asp Glu Phe Asp Glu Val Leu Leu Lys Ala Glu Ala
660 665 670

10 Ile Leu Lys Pro Ile Trp His Tyr Leu His Ala Pro Asn Thr Pro Leu
675 680 685

15 His Tyr Glu Leu Arg Glu Asp Lys Leu Leu Leu Ala Glu His Cys Val
690 695 700

Ser Glu Met Pro Ala Arg Gln Ala Phe Ile Glu Pro
705 710 715

20 <210> 43
<211> 137
<212> PRT
<213> Xanthomonas albilineans

25 <400> 43

30 Met Arg Pro Pro Arg Leu Arg Ala Asn Gln Asp Gly Leu Leu Met Asp
1 5 10 15

Thr Ala Gly Arg Val Val Glu Gly Cys Thr Ser Asn Leu Phe Leu Val
20 25 30

35 Glu Asn Gly His Leu Val Thr Pro Asp Leu Gly Val Ala Gly Val Ser
35 40 45

40 Gly Ile Met Arg Gly Arg Val Ile Glu Tyr Gly Arg Gln His Gly Leu
50 55 60

Ala Cys Ala Val Lys His Val Tyr Pro Asp Gln Leu Val Arg Ala Gln
65 70 75 80

5
Glu Val Phe Leu Thr Asn Ala Val Phe Gly Ile Leu Leu Val Arg Ser
85 90 95

10
Ile Asp Ala His Ser Tyr Arg Ile Asp Pro Val Thr Leu Arg Leu Leu
100 105 110

15
Asp Ala Leu Cys Gln Gly Val Tyr Phe Thr Glu Arg Ser Leu His Gln
115 120 125

20
Val Ser Thr His Ala Gly Gln Asp Pro
130 135

25
<210> 44
<211> 200
<212> PRT
<213> Xanthomonas albilineans
<400> 44

30
Met Pro Ala Lys Thr Leu Glu Ser Lys Asp Tyr Cys Gly Glu Ser Phe
1 5 10 15

35
Val Ser Glu Asp Arg Ser Gly Gln Ser Leu Glu Ser Ile Arg Phe Glu
20 25 30

40
Asp Cys Thr Phe Arg Gln Cys Asn Phe Thr Glu Ala Glu Leu Asn Arg
35 40 45

40
Cys Lys Phe Arg Glu Cys Glu Phe Val Asp Cys Asn Leu Ser Leu Ile

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	50		55		60
5	Ser Ile Pro Gln Thr Ser Phe Met Glu Val Arg Phe Val Asp Cys Lys				
	65		70		75 80
10	Met Leu Gly Val Asn Trp Thr Ser Ala Gln Trp Pro Ser Val Lys Met				
		85		90	95
15	Glu Gly Ala Leu Ser Phe Glu Arg Cys Ile Leu Asn Asp Ser Leu Phe				
	100		105		110
20	Tyr Gly Leu Tyr Leu Ala Gly Val Lys Met Val Glu Cys Arg Ile His				
	115		120		125
25	Asp Ala Asn Phe Thr Glu Ala Asp Cys Glu Asp Ala Asp Phe Thr Gln				
	130		135		140
30	Ser Asp Leu Lys Gly Ser Thr Phe His Asn Thr Lys Leu Thr Gly Ala				
	145		150		155 160
35	Ser Phe Ile Asp Ala Val Asn Tyr His Ile Asp Ile Phe His Asn Asp				
		165		170	175
40	Ile Lys Arg Ala Arg Phe Ser Leu Pro Glu Ala Ala Ser Leu Leu Asn				
		180		185	190
	Ser Leu Asp Ile Glu Leu Ser Asp				
	195		200		
	<210> 45				
	<211> 202				

<212> PRT

<213> Xanthomonas albilineans

<400> 45

5

Met His Pro Pro Ser Pro Leu Asn Thr Gln Gln Lys Asp Trp Leu Thr
1 5 10 15

10

Arg Gly Gly Ser Leu Thr Ala His Leu Arg Leu Leu Gly Gln Val Gln
20 25 30

15

Val Gln Val Gln Arg Glu His Lys Ser Met Ala Trp Leu Asp Glu Tyr
35 40 45

20

Arg Val Leu Gly Leu Ser Arg Cys Leu Leu Val Trp Val Arg Glu Val
50 55 60

25

Val Leu Val Val Asp Ala Lys Pro Tyr Val Tyr Ala Arg Ser Leu Thr
65 70 75 80

Pro Leu Thr Ala Ser Tyr Asn Ala Trp Gln Ala Val Arg Ser Ile Gly
85 90 95

30

Ser Arg Pro Leu Ala Asp Leu Leu Phe Arg Asp Arg Ser Val Leu Arg
100 105 110

35

Ser Ala Leu Ala Ser Arg Arg Ile Thr Ala Gln His Pro Leu His Arg
115 120 125

40

Arg Ala Cys Asn Phe Val Ala Gln Ser His Ala Thr Gln Ala Leu Leu
130 135 140

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Ala Arg Arg Ser Val Phe Thr Arg Gln Gly Ala Pro Leu Leu Ile Thr
 145 150 155 160

5 Glu Cys Met Leu Pro Ala Leu Trp Ala Thr Leu Glu Pro Val Ala Ala
 165 170 175

10 Pro Arg Gln Ala Ser Leu Ser Ala Asp Gly Pro Cys Arg His Ser Ala
 180 185 190

15 Gln Ile Val Ser Pro Glu Ser Met Leu Glu
 195 200

<210> 46
 <211> 278
 <212> PRT
 20 <213> Xanthomonas albilineans

<400> 46

25 Met Pro Asn Ala Val Pro Met Gln Gly Ala Arg Gly Leu Pro Gln Pro
 1 5 10 15

30 Gln Ala Met Asn Pro Gly Leu Pro Ser Val Gly Gly Leu Ser Ala Gly
 20 25 30

Gln Pro Leu Gln Leu Ser Leu Ala Pro Glu Leu Gln Ala Ala Ala Arg
 35 40 45

35 Ser Ala His Arg His Leu Leu Asp Asp Gly Thr Ala Leu Tyr Leu Leu
 50 55 60

40 Ala Phe Asp Thr Ala Gln Phe Asp Pro Gly Ala Phe Ala Ala Met Ala
 65 70 75 80

Ile Ala Arg Pro Asp Ser Ile Ala Arg Ser Val Arg Lys Arg Gln Ala
85 90 95

5
Glu Phe Leu Phe Gly Arg Leu Ala Ala Arg Leu Ala Leu Gln Glu Val
100 105 110

10
Leu Gly Pro Ala Gln Ala Gln Ala Asp Ile Ala Ile Gly Ala Thr Arg
115 120 125

15
Ala Pro Cys Trp Pro Ala Gly Ser Leu Gly Ser Ile Ser His Cys Glu
130 135 140

20
Asp Tyr Ala Ala Ala Ile Ala Met Ala Ala Gly Thr Arg His Gly Val
145 150 155 160

Gly Ile Asp Leu Glu Arg Pro Ile Thr Pro Ala Ala Arg Ala Ala Leu
165 170 175

25
Leu Ser Ile Ala Ile Asp Ala Asp Glu Ala Ala Arg Leu Ala Lys Ala
180 185 190

30
Ala Asp Ala Gln Trp Pro Gln Asp Leu Leu Leu Thr Ala Leu Phe Ser
195 200 205

35
Ala Lys Glu Ser Leu Phe Lys Ala Ala Tyr Ser Ala Val Gly Arg Tyr
210 215 220

40
Phe Asp Phe Ser Ala Ala Arg Leu Cys Gly Ile Asp Leu Ala Arg Gln
225 230 235 240

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Cys Leu His Leu Arg Leu Thr Glu Thr Leu Cys Ala Gln Phe Val Ala
 245 250 255

5 Gly Gln Val Cys Glu Val Gly Phe Ala Arg Leu Pro Pro Asp Leu Val
 260 265 270

10 Leu Thr His Tyr Ala Trp
 275

<210> 47
 <211> 634
 15 <212> PRT
 <213> Xanthomonas albilineans
 <400> 47

20 Met Ser Val Glu Thr Gln Lys Glu Thr Leu Gly Phe Gln Thr Glu Val
 1 5 10 15

25 Lys Gln Leu Leu Gln Leu Met Ile His Ser Leu Tyr Ser Asn Lys Glu
 20 25 30

Ile Phe Leu Arg Glu Leu Ile Ser Asn Ala Ser Asp Ala Ala Asp Lys
 30 35 40 45

Leu Arg Phe Glu Ala Leu Val Lys Pro Glu Leu Leu Asp Gly Asp Ala
 50 55 60

35 Gln Leu Arg Ile Arg Ile Gly Phe Asp Lys Asp Ala Gly Thr Val Thr
 65 70 75 80

40 Ile Asp Asp Asn Gly Ile Gly Met Ser Arg Glu Glu Ile Val Ala His
 85 90 95

Leu Gly Thr Ile Ala Lys Ser Gly Thr Ser Asp Phe Leu Lys His Leu
100 105 110

5 Ser Gly Asp Gln Lys Lys Asp Ser His Leu Ile Gly Gln Phe Gly Val
115 120 125

10 Gly Phe Tyr Ser Ala Phe Ile Val Ala Asp Gln Val Asp Val Tyr Ser
130 135 140

15 Arg Arg Ala Gly Leu Pro Ala Ser Asp Gly Val His Trp Ser Ser Arg
145 150 155 160

20 Gly Glu Gly Glu Phe Glu Val Ala Thr Ile Asp Lys Pro Glu Arg Gly
165 170 175

Thr Arg Ile Val Leu His Leu Lys Glu Glu Glu Lys Gly Phe Ala Asp
180 185 190

25 Gly Trp Lys Leu Arg Ser Ile Val Arg Lys Tyr Ser Asp His Ile Ala
195 200 205

30 Leu Pro Ile Glu Leu Ile Lys Glu His Tyr Gly Glu Asp Lys Asp Lys
210 215 220

35 Pro Glu Thr Pro Glu Trp Glu Thr Val Asn Arg Ala Ser Ala Leu Trp
225 230 235 240

40 Thr Arg Pro Arg Thr Glu Ile Lys Asp Glu Glu Tyr Gln Glu Leu Tyr
245 250 255

	Lys His Ile Ala His Asp His Glu Asn Pro Val Ala Trp Ser His Asn
	260 265 270
5	Lys Val Glu Gly Lys Leu Glu Tyr Thr Ser Leu Leu Tyr Leu Pro Gly
	275 280 285
10	Arg Ala Pro Phe Asp Leu Tyr Gln Arg Asp Ala Ser Arg Gly Leu Lys
	290 295 300
15	Leu Tyr Val Gln Arg Val Phe Ile Met Asp Gln Ala Asp Gln Phe Leu
	305 310 315 320
	Pro Leu Tyr Leu Arg Phe Ile Lys Gly Ile Val Asp Ser Ser Asp Leu
	325 330 335
20	Pro Leu Asn Val Ser Arg Glu Ile Leu Gln Ser Gly Pro Val Ile Asp
	340 345 350
25	Ser Met Lys Ser Ala Leu Thr Lys Arg Ala Leu Asp Met Leu Glu Lys
	355 360 365
30	Leu Ala Lys Asp Asp Pro Glu Arg Tyr Lys Gly Val Trp Lys Asn Phe
	370 375 380
35	Gly Gln Val Leu Lys Glu Gly Pro Ala Gln Asp Phe Gly Asn Arg Glu
	385 390 395 400
	Lys Ile Ala Gly Leu Leu Arg Phe Ala Ser Thr His Ser Gly Asp Asp
	405 410 415
40	Ala Gln Asn Val Ser Leu Ala Asp Tyr Val Ala Arg Met Lys Asp Gly

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	420	425	430
5	Gln Asp Lys Leu Tyr Tyr Leu Thr Gly Glu Ser Tyr Ala Gln Ile Lys 435 440 445		
10	Asp Ser Pro His Leu Glu Val Phe Arg Lys Lys Gly Ile Glu Val Leu 450 455 460		
	Leu Leu Thr Asp Arg Ile Asp Glu Trp Leu Met Ser Tyr Leu Thr Glu 465 470 475 480		
15	Phe Asp Ser Lys Ser Phe Val Asp Val Ala Arg Gly Asp Leu Asp Leu 485 490 495		
20	Gly Lys Leu Asp Ser Glu Glu Glu Lys Gln Ala Gln Glu Glu Ala Ala 500 505 510		
25	Lys Ala Lys Gln Gly Leu Ala Glu Arg Ile Gln Gln Val Leu Lys Asp 515 520 525		
30	Glu Val Ala Glu Val Arg Val Ser His Arg Leu Thr Asp Ser Pro Ala 530 535 540		
	Ile Leu Ala Ile Gly Gln Gly Asp Met Gly Leu Gln Met Arg Gln Ile 545 550 555 560		
35	Leu Glu Ala Ser Gly Gln Lys Leu Pro Glu Ser Lys Pro Val Phe Glu 565 570 575		
40	Phe Asn Pro Ala His Pro Leu Ile Glu Lys Leu Asp Ala Glu Pro Asp 580 585 590		

Val Asp Arg Phe Gly Asp Leu Ala Arg Val Leu Phe Asp Gln Ala Ala
595 600 605

5

Leu Ala Ala Gly Asp Ser Leu Lys Asp Pro Ala Ala Tyr Val Arg Arg
610 615 620

10

Leu Asn Lys Leu Leu Leu Glu Leu Ser Ala
625 630

15

<210> 48
<211> 20
<212> DNA
<213> Xanthomonas albilineans

20

<400> 48
gcgtaccggt gtccagtagg 20

25

<210> 49
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<212> DNA
<213> Xanthomonas albilineans

30

<400> 49
gctggaaacc gagaatctga 20

35

<210> 50
<211> 20
<212> DNA
<213> Xanthomonas albilineans

40

<400> 50
gacacgatca gccgctagga 20

<210> 51

CLAIMS:

5

We claim:

- 1 1. DNA molecules encoding the Albicidin Biosynthetic Gene Clusters and
2 proteins selected from the group consisting of:
3 (a) isolated DNA fragments which encode proteins that in turn
4 individually and collectively perform functions in Albicidin Biosynthesis;
5 (b) isolated DNA which hybridizes to isolated DNA of (a) above and that
6 encodes a protein that in turn performs an individual function in Albicidin
7 Biosynthesis; and
8 (c) isolated DNA differing from the isolated DNAs of (a) and (b) above
9 in codon sequence due to the degeneracy of the genetic code, and which encodes
10 a protein that in turn performs as function in Albicidin Biosynthesis
11 (d) isolated DNA selected from the group of DNA molecules having a
12 sequence that is at least 70% homologous with a DNA comprising one or more
13 of SEQ. ID. Nos.1 to 25.
- 1 2. Isolated DNA molecules of claim 1 comprising any one of SEQ ID No.1, SEQ
2 ID No. 2 or SEQ ID No. 3.
- 1 3. A vector comprising a purified and isolated DNA molecule(s) of claim 1
2 operably linked to promoters.
- 1 4. A host cell comprising an isolated DNA molecule of claim 1.
- 1 5. A host cell comprising the isolated DNA molecule of claim 2.
- 1 6. A host cell comprising a vector of claim 3.

- 1 7. A method of producing a protein, wherein said protein consists of an amino
2 acid sequence selected from the group consisting of SEQ ID Nos. 26 to 48,
3 comprising the steps of: expressing DNA molecules of Claim 1 in a host cell,
4 wherein said DNA molecules encodes a protein, and wherein the expression of
5 said DNA molecules leads to the production of Albicidins by said cell.

- 1 8. A method of producing a polyketide carrying para-aminobenzoic acid and/or
2 carbamoyl benzoic acid by inserting at least one DNA Fragment of Claim 1
3 that encodes a PKS protein into a cell and causing the cell to express the
4 encoded PKS protein under conditions such that the PKS protein functions to
5 produce a polyketide carrying either a para-aminobenzoic acid or a carbamoyl
6 benzoic acid or both.

- 1 9. A method of producing polyketide/peptides carrying para-aminobenzoic acid
2 and/or carbamoyl benzoic acid by inserting at least one DNA Fragment of
3 Claim 1 that encodes a PKS protein into a cell and causing the cell to express
4 the encoded PKS protein under conditions such that the PKS protein functions
5 to produce a polyketide carrying either a para-aminobenzoic acid or a
6 carbamoyl benzoic acid or both.

- 1 10. A method of activating nonproteinogenic amino acids like paraminobenzoic
2 acid and/or carbamoyl benzoic acid for incorporation into peptides or
3 polyketides by inserting at least one DNA Fragment of Claim 1 that encodes a
4 PKS protein into a cell and causing the cell to express the encoded PKS protein
5 under conditions such that the PKS protein functions to produce a polyketide
6 carrying either a para-aminobenzoic acid or a carbamoyl benzoic acid or both.

- 1 11. Proteins encoded by the DNA of Claim 1.

- 1 12. Proteins encoded by the DNA of Claim 2.

- 1 13. An isolated and purified antibiotic produced by a process that includes at least
2 three proteins coded by DNA sequences of claim 1 in combination with
3 additional enzymes that modify the product to provide a non-naturally

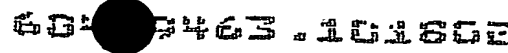
- 1 occurring Albicidin-like product having at least one of the useful properties
2 reported for albicidin.
- 1 14. An antibiotic or antibiotics of claim 13 having at least one of the general
2 structures illustrated in Figure 11.
- 1 15. An antibiotic produced by the process of expressing the DNA of one or more
2 of the genes included in the Albicidin Biosynthetic Gene Clusters of Claim 1 in
3 a genetically modified host cell sustained in a culture media, and thereafter
4 separating the antibiotic from the host cell and culture media.
- 1 16. A process for producing an antibiotic that comprises modifying a host cell to
2 enhance expression of the DNA of claim 1 by insertion of expression
3 enhancing DNA into the genome of a *Xanthomonas albilineans* strain,
4 *Escherichia coli* strain, or other Albicidin producing microbial strain, in a
5 position operative to enhance expression of the enzymes of the Albicidin
6 Biosynthetic Gene Clusters, culturing the modified host cell to produce an
7 antibiotic and isolating the antibiotic.
- 1 17. An isolated purified antibiotic having at least 4 of the structural elements
2 illustrated in Figure 11, and an elemental composition of $C_{40}H_{35}N_6O_{15}$.
- 1 18. A method of protecting a plant against damage from albicidin that comprises
2 applying an agent that blocks expression at least one gene in the Albicidin
3 Biosynthetic Gene Clusters of claim 1 to the plant to be protected.
- 1 19. A method of obtaining agents useful in blocking expression of albicidin by
2 screening materials against a modified host cell line that expresses the
3 Albicidin Biosynthesis Gene Clusters of claim 1 and selecting for materials
4 that stop or decrease albicidin production.
- 1 20. A method of protecting a plant against phytotoxic damage from an antibiotic
2 that comprises inserting into the plant and operably expressing at least one

1 resistance gene from the Albicidin Biosynthesis Gene Clusters of claim 1 in
2 the plant to be protected.

1 21. A plant reproductive part carrying an albicidin resistance gene of claim 1
2 selected from the group consisting of seeds, propagative materials and plant
3 parts.

ABSTRACT

5 Three gene clusters that together encode albicidin biosynthesis, the complete gene DNA sequences, the deduced protein sequences for the enzymes and methods for using the DNA sequences are disclosed and discussed as well as methods for plant protection and creating new antibiotics. The novel Albicidin family of antibiotics is disclosed and their structure deduced.



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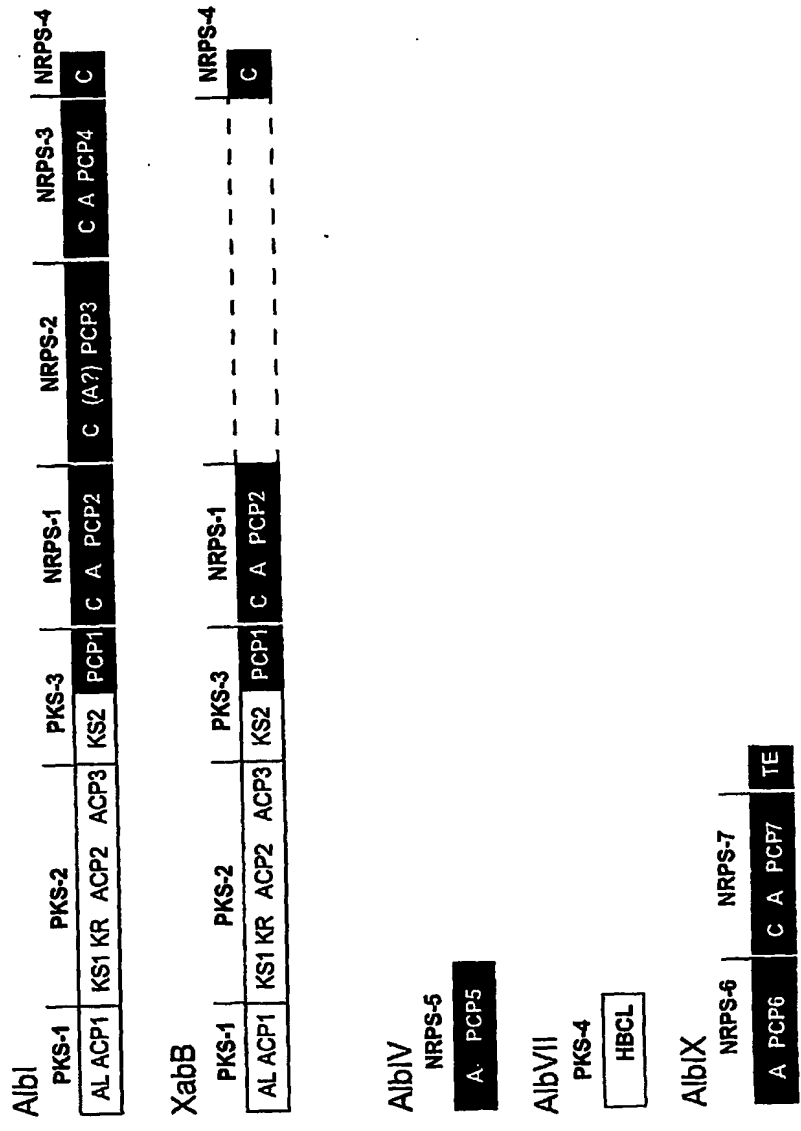


Figure 2

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Sgl-TcmO	173	FVDLGARG	234	PRADVFIV	263	ALTPGGAVLV
Sgl-TcmN	331	IADLGGGDG	393	TGYDAYLF	423	IGDDARLLI
Smy-MdmC	64	VLEIGTFIG	135	GAFDIVFV	159	LVRPGGLVAI
Mxa-SafC	63	TLEVGVFTG	134	GTFDLAFI	158	LVRPGGLIIL
Ser-EryG	85	VLDVGFGLG	149	ETFDRTVS	178	VLKPGGVLAI
Spe-DauK	183	VLDVGGGKG	254	RKADAIIIL	273	ALEPGGRILI
Sal-DmpM	208	VVDIGGADG	269	GGGDLIVL	298	AMPAHARLV
Shy-RapM	106	VLEVGCIMG	155	VQDAEEL	194	ALRRGGALSH
Sav-AveD	71	VLDVGCSSG	124	GSFDAAWA	151	VLKPGGRLAV
Sar-Cmet	158	VLDVACGHG	220	GPYDLSLI	251	ATPFGGRIGI
AlbII	174	VLDVAAGHG	236	SGYDVILL	267	ALNDDGMVIT
		Motif I		Motif II		Motif III

Figure 3



[illegible]

Figure 6

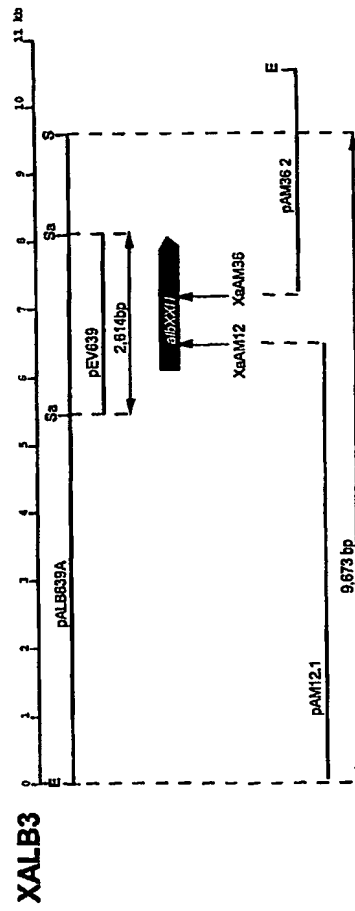
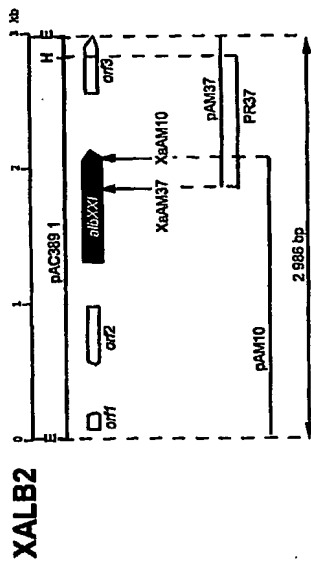


Figure 8

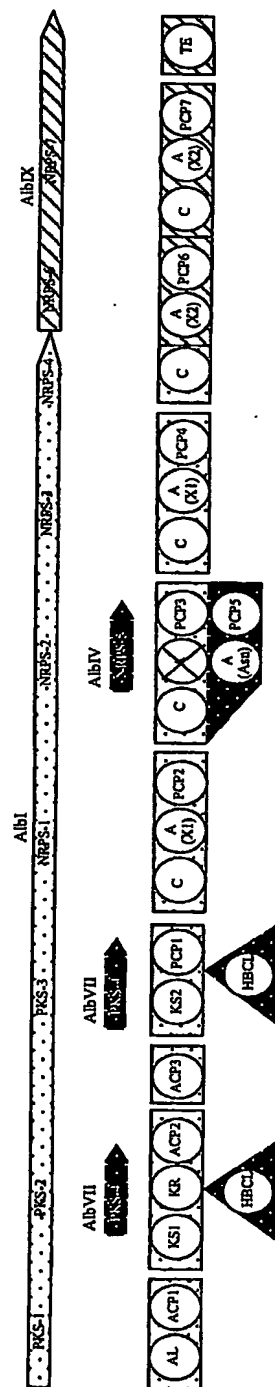


Figure 9A

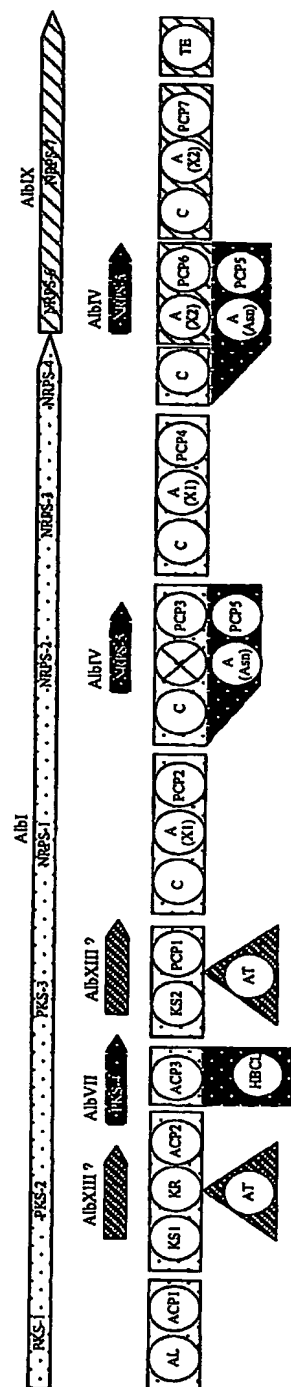


Figure 9B

Rifa-1 LGRVDVLQPA CFAMVGLAAVWESVGVVRPD AVVGH SQGEI
Rifa-2 LDQMTYTQGA LFAVETALFRLFESWGVVRPGLLAGHSIGEL
Rifa-3 LDRVDVVQPA SFAMVGLAAVWTSLSGVT PD AVVGH SQGEI
RifB-1 LDRVDVVQPA SFAMVGLAAVWESVGVVRPD AVVGH SQGEI
Rife-1 LNQT VFTGAGLFAVESALFRLAESWGVVRPD VVIGH SIGEL
BlmVIII ADDTRAAQPALFAVEYALARTLMDWGVVRP AAPMLGHSLGEV

Figure 10A

AlbxIII LEDRPRHIRAVIDTLTGHAQFGPAIQAHNVAVIGH SVGGY
FenF TRTMNAQPA IITVSVIAYQVVMQEI GIKPHFLAGHSIGY
LipA PDSRGRQLLAALDYLTRSSVVRGRIDSGRLGVMGHSMGGG

Figure 10B

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99

Figure 11A: Putative substrates of FKS and NRPS. The diagram illustrates the biosynthetic pathways for various compounds, categorized by the type of enzyme involved: PKS (Polyketide Synthase) and NRPS (Non-ribosomal Peptide Synthetase).

PKS Pathway:

- PKS-1:** AL (Acyl-CoA) → ACP1 → KS1 → NR → ACP2 → ACP3. Substrate: CC(=O)S (Acetyl-CoA).
- PKS-2:** KS2 → ACP2 → ACP3. Substrate: CC(=O)CC(=O)S (Malonyl-CoA).
- PKS-3:** KS2 → ACP2 → ACP3. Substrate: CC(=O)CC(=O)S (Malonyl-CoA).

NRPS Pathway:

- NRPS-1:** C → A → PCP2 → C → A → PCP2. Substrate: NC(=O)c1ccccc1 (para-aminobenzoate (hypothesis 1) or carbamoyl benzoate (hypothesis 2)).
- NRPS-2:** C → A → PCP2 → C → A → PCP2. Substrate: NC(=O)CC(=O)S (asparagine).
- NRPS-3:** C → A → PCP2 → C → A → PCP2. Substrate: NC(=O)c1ccccc1 (para-aminobenzoate (hypothesis 1) or carbamoyl benzoate (hypothesis 2)).
- NRPS-4:** C → A → PCP2 → C → A → PCP2. Substrate: NC(=O)c1ccccc1 (para-aminobenzoate (hypothesis 1) or carbamoyl benzoate (hypothesis 2)).
- NRPS-5:** C → A → PCP2 → C → A → PCP2. Substrate: NC(=O)c1ccccc1 (para-aminobenzoate (hypothesis 1) or carbamoyl benzoate (hypothesis 2)).
- NRPS-6:** C → A → PCP2 → C → A → PCP2. Substrate: NC(=O)c1ccccc1 (para-aminobenzoate (hypothesis 1) or carbamoyl benzoate (hypothesis 2)).
- NRPS-7:** C → A → PCP2 → C → A → PCP2. Substrate: NC(=O)c1ccccc1 (para-aminobenzoate (hypothesis 1) or carbamoyl benzoate (hypothesis 2)).

Albiv Pathway:

- Albiv:** NRPS-3 → NRPS-2 → NRPS-1. Substrate: NC(=O)c1ccccc1 (para-aminobenzoate (hypothesis 1) or carbamoyl benzoate (hypothesis 2)).

TE Pathway:

- TE:** C → A → PCP2 → C → A → PCP2. Substrate: NC(=O)c1ccccc1 (para-aminobenzoate (hypothesis 1) or carbamoyl benzoate (hypothesis 2)).

Steps 1 to 8:

- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8